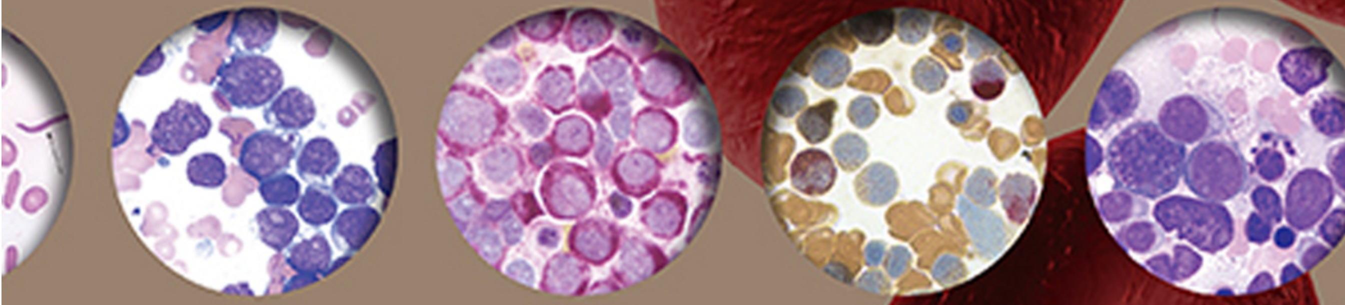
ANDERSON'S
Atlas of Hematology

SECOND EDITION

SHAUNA C. ANDERSON YOUNG
KEILA B. POULSEN



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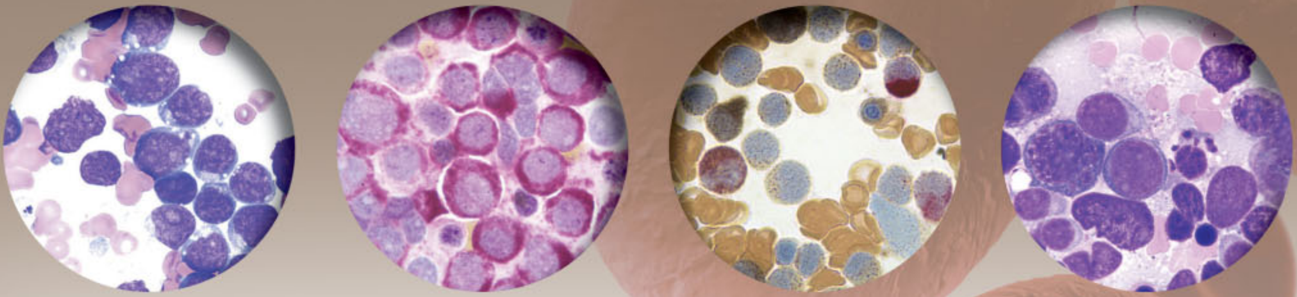

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Preface

After many years of interacting with students, Shauna Anderson Young and Keila Poulsen have produced this atlas to accompany the interactive tools, ***Anderson's Electronic Atlas of Hematology and Anderson's Electronic Atlas of Hematologic Disorders.*** High-quality images are combined with in-depth descriptive text to create an ideal bench-top tool for the student and practitioner.

ORGANIZATION

The text has two units: Cell Descriptions (or normal hematology) and Hematologic Disorders. The first unit is organized into three parts:

- Hematopoietic cells, including a comparison of some of the commonly confused cells
- Bone marrow cellularity, cells of the reticuloendothelial system, and nonhematopoietic cells
- Cytochemical stains

Each cell description includes the cell size, a description of the nucleus and cytoplasm, and a list of associated clinical conditions. A drawing of the maturation series for each cell type accompanies the high-quality photographs.

The second unit describes hematologic disorders. Each description includes a brief summary of the clinical features, pathology, laboratory features, and a diagnostic scheme. The diagnostic scheme summarizes the relevant laboratory findings that lead to the features of a particular disorder. This unit is also organized into three parts:

- Red blood cell disorders
- White cell disorders
- Miscellaneous disorders

The WHO classification of hematopoietic and lymphoid tissue has been incorporated into this atlas.

IS THIS TEXT FOR YOU?

Yes! The atlas can be used to teach any level of hematology. Whether it is used for teaching cell identification or for the diagnosis of disease, it is a valuable learning tool for students in medical laboratory technician or medical laboratory science programs. It is also a great reference for students in nursing and nurse practitioner programs, as well as medical students or residents. Finally, this spiral-bound atlas is an ideal, user-friendly, convenient companion at the microscope and can be used as a retraining resource or as a laboratory reference.

ADDITIONAL RESOURCES

Anderson's Atlas of Hematology, Second Edition, includes additional resources for both instructors and students that are available on the book's companion Website at http://thePoint.lww.com/Andersonatlas2e.

Instructor Resources

Approved adopting instructors will be given access to the following additional resources:

- Image Bank

Student Resources

Students who have purchased Anderson's Atlas of Hematology, Second Edition, have access to the following additional resources:

Interactive Atlas of Hematology

- Over 900 high-quality images
- Side-by-side viewing for comparison of cells
- On/off labeling function
- Over 100 morphology evaluation questions with instant feedback and rationale
- Key terms linked to Stedman's Medical Dictionary

Interactive Atlas of Hematologic Disorders

- Over 500 high-quality images
- Concept applications for each disorder
- Image-driven case studies
- Multiple choice question exam with answer rationale
- Key terms linked to Stedman's Medical Dictionary

In addition, purchasers of the text can access the searchable full text online by going to the Anderson's Atlas of Hematology, Second Edition, Website at http://thePoint.lww.com/Andersonatlas2e. See the inside front cover of this text for more details, including the passcode you will need to gain access to the Website.

Acknowledgments

We would like to thank our families for their support because this project required an incredible time commitment. Our students have always been a source of stimulus and enjoyment. We would like to thank them for their suggestions and our colleagues for their contributions.

Shauna C. Anderson Young
Keila B. Poulsen

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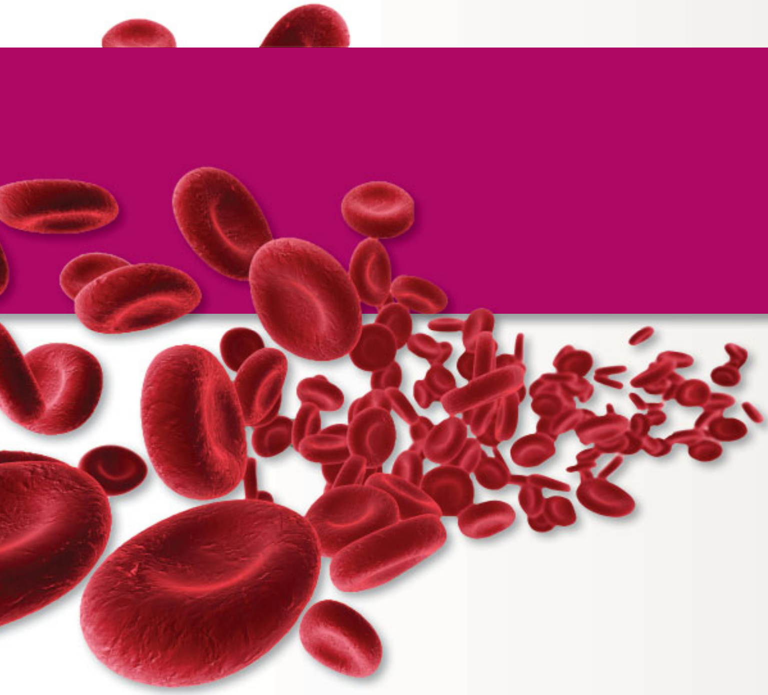


Unit I

Cell Descriptions

- *Section A* Blood Cells
- *Section B* Bone Marrow
- *Section C* Cytochemistry

Section A

Blood Cells

CHAPTER 1

Red Blood Cells

NORMAL MATURATION SERIES

Erythrocyte Series

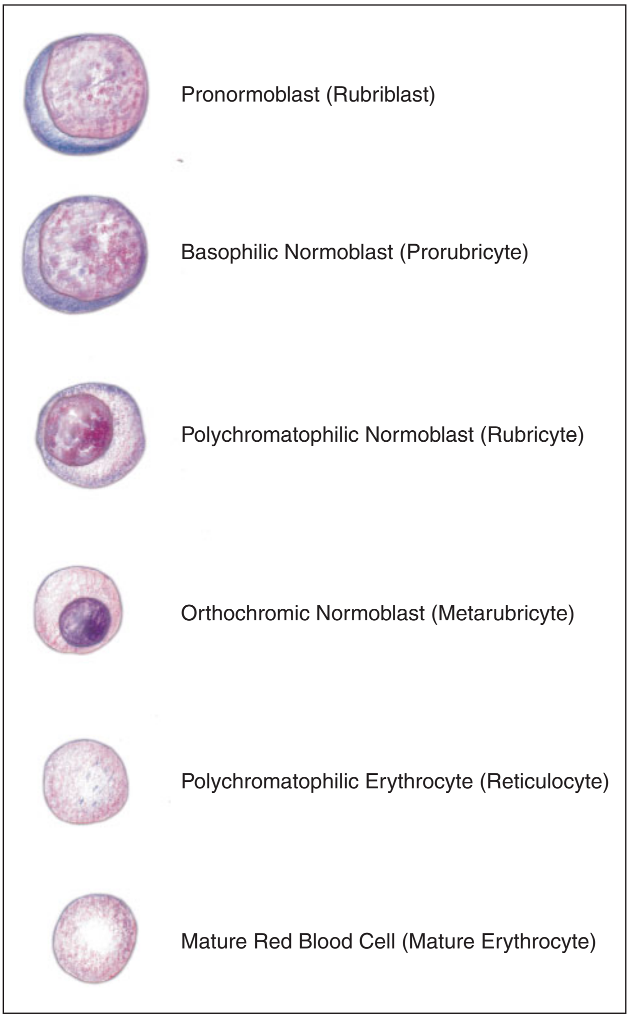

Pronormoblast (Rubriblast)
Basophilic Normoblast (Prorubricyte)
Polychromatophilic Normoblast (Rubricyte)
Orthochromic Normoblast (Metarubricyte)
Polychromatophilic Erythrocyte (Reticulocyte)
Mature Red Blood Cell (Mature Erythrocyte)

Figure IA1-1

Pronormoblast (Rubriblast)

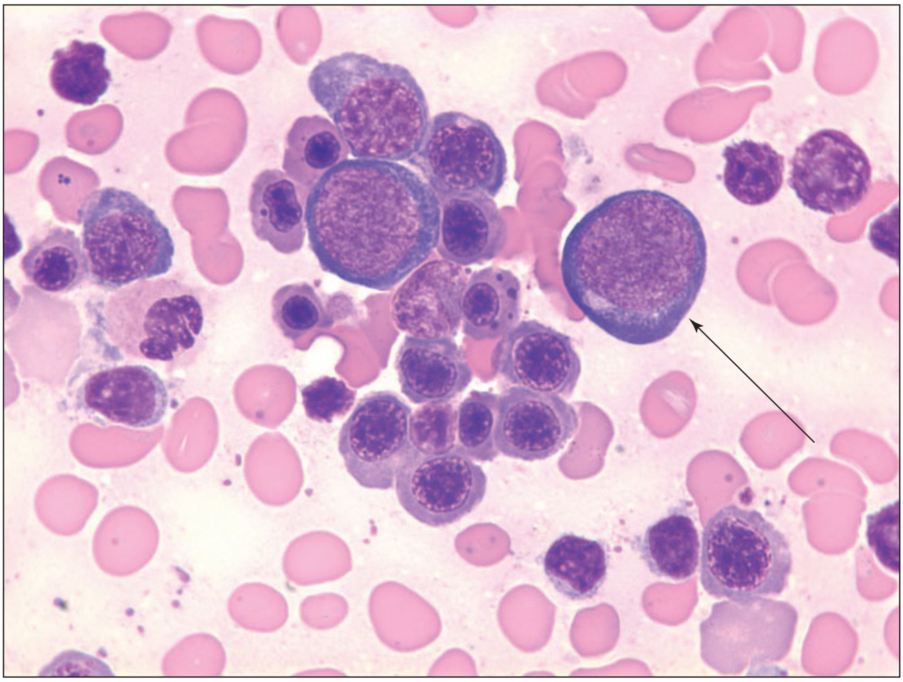


Figure IA1-2

Size: 14–22 µ

Nucleus

Shape: Round to slightly oval
N/C Ratio: 5:1–8:1
Color: Purple-red
Chromatin: Fine, but granular; parachromatin sparse
Nucleoli: 1–2 prominent which may show a bluish tint

Cytoplasm

Color: Deep blue
Contents: Golgi, mitochondria, which produce a lighter blue color (perinuclear halo)

Clinical Conditions

- Erythroleukemia (FAB–M6a)
- Pure erythroid leukemia (FAB–M6b)
- Acute erythroid leukemia (WHO)
- Hemolytic disease of the newborn

Basophilic Normoblast (Prorubricyte)

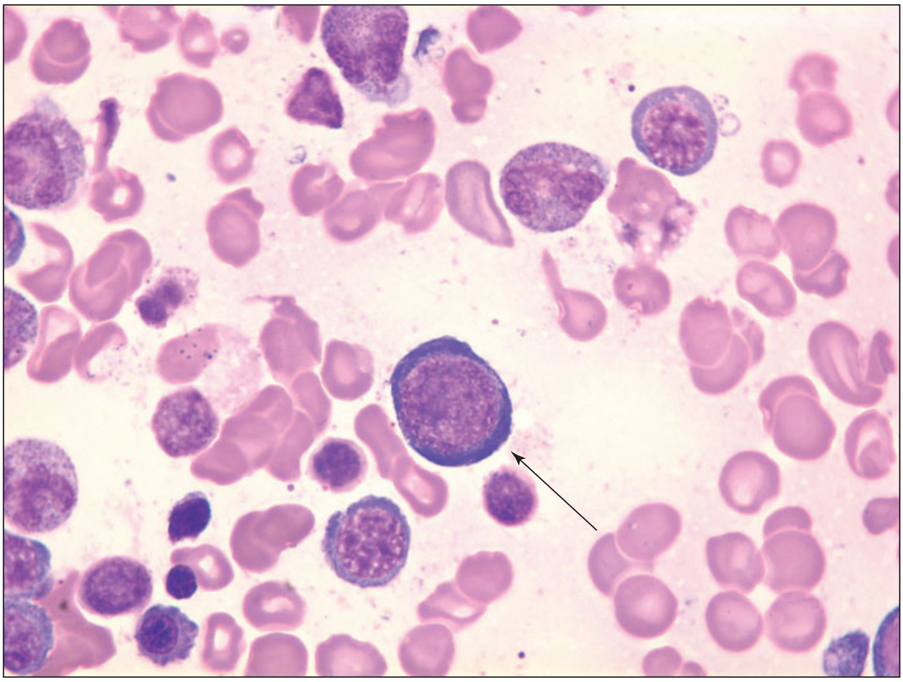


Figure IA1-3

Size: 12–17 µ

Nucleus

Shape: Round, centered
N/C Ratio: 4:1–6:1
Color: Purple interspersed with light areas
Chromatin: Coarse and somewhat condensed
Nucleoli: Usually not visible

Cytoplasm

Color: Deep blue
Contents: Golgi may produce a light blue area near the nucleus, many mitochondria

Clinical Conditions

- Erythroleukemia (FAB–M6a)
- Pure erythroid leukemia (FAB–M6b)
- Hemolytic disease of the newborn
- Acute erythroid leukemia (WHO)

Polychromatophilic Normoblast (Rubricyte)

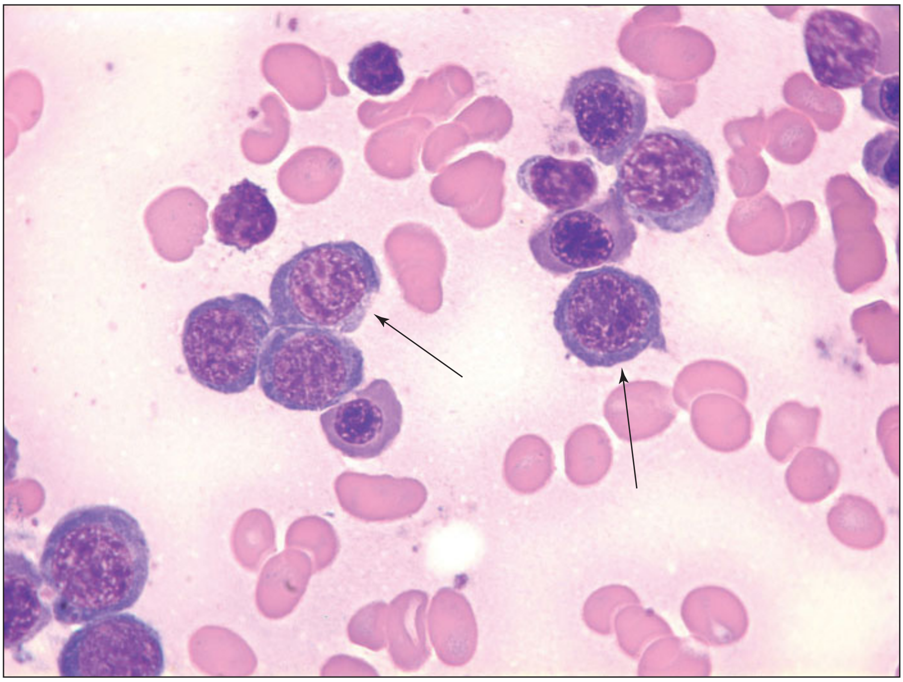


Figure IA1-4

Size: 11–14 μ

Nucleus

Shape: Round, centered to eccentric
N/C Ratio: 1:1–4:1
Color: Red-purple
Chromatin: Coarse and condensed; parachromatin distinct, producing a "checkerboard" appearance
Nucleoli: None

Cytoplasm

Color: Bluish-pink to grey-blue
Contents: Perinuclear halo visible; increased hemoglobin, causing the pink-grey color; decreased RNA, causing the lighter blue color

Clinical Conditions

- Erythroleukemia (FAB–M6a)
- Pure erythroid leukemia (FAB–M6b)
- Hemolytic disease of the newborn
- Primary myelofibrosis (PMF)
- Chronic myelocytic leukemia (CML)
- Hemolytic anemias
- Thalassemia major
- Sickle cell disease
- Acute erythroid leukemia (WHO)

Orthochromic Normoblast (Metarubricyte)

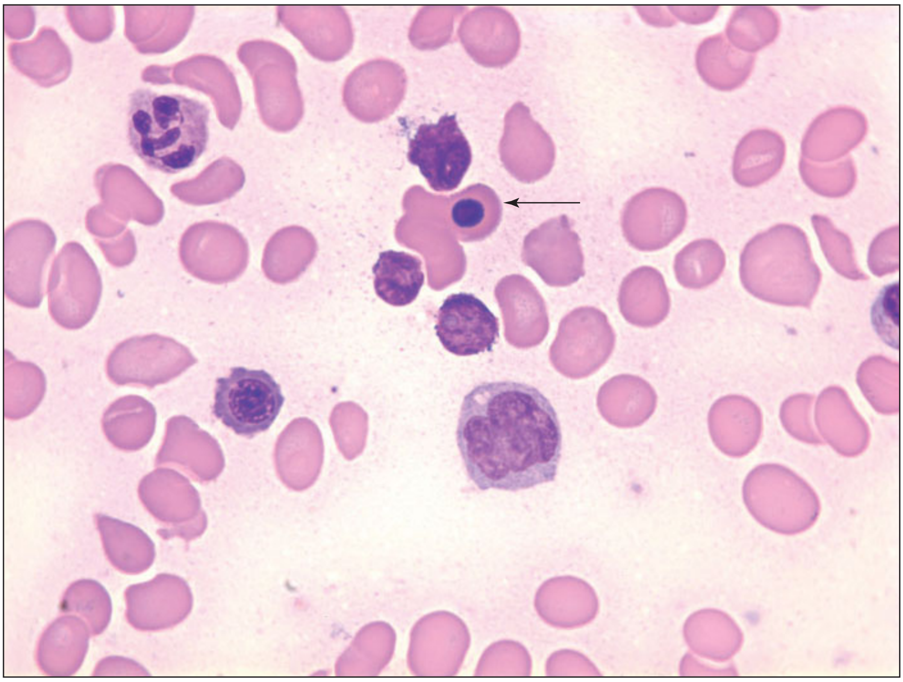


Figure IA1-5

Size: 8–12 μ

Nucleus

Shape: Round, centered to eccentric; may be fragmented or extruding
N/C Ratio: 1:4–1:2
Color: Blue-purple
Chromatin: Condensed and homogeneous (pyknotic)
Nucleoli: None

Cytoplasm

Color: Pink to orange-pink, with a hint of blue
Contents: Hemoglobin production increased

Clinical Conditions

- Erythroleukemia (FAB–M6a)
- Pure erythroid leukemia (FAB–M6b)
- Acute erythroid leukemia (WHO)
- Hemolytic disease of the newborn
- Myeloproliferative diseases—PMF, CML
- Myelodysplastic syndromes
- Thalassemia major
- Sickle cell disease

Polychromatophilic Erythrocyte (Reticulocyte)

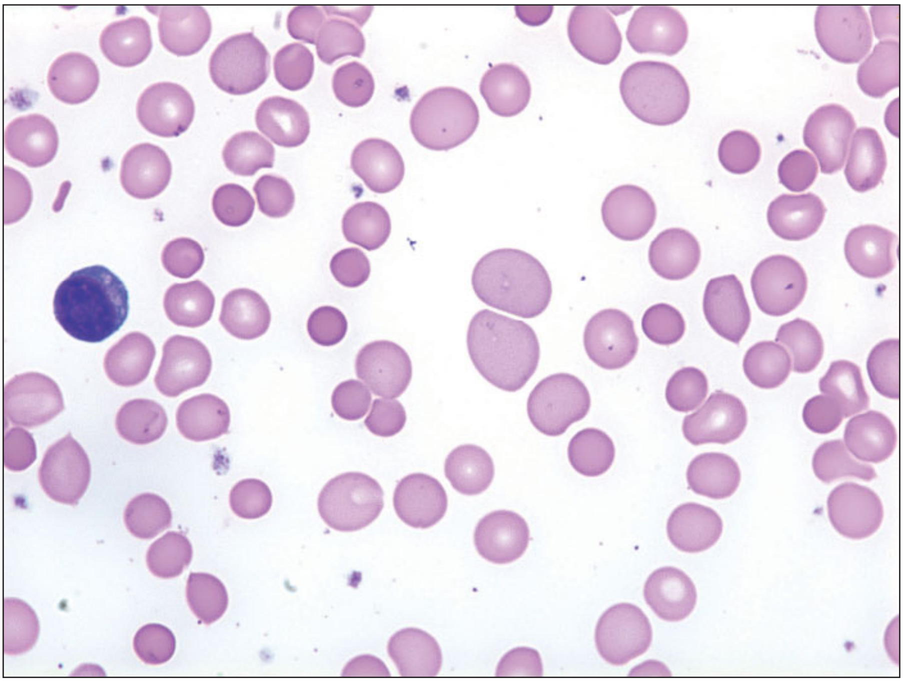


Figure IA1-6

Size: 8–11 µ

Nucleus

None

Cytoplasm

Color: Pink, with a tint of blue
Contents: Remnants of Golgi and mitochondria, residual RNA (reticulum)

Clinical Conditions

- Increased erythrocyte production
- Hemolytic anemias
- Membrane disorders
- Hemolytic disease of the newborn

Mature Red Blood Cell (Mature Erythrocyte)

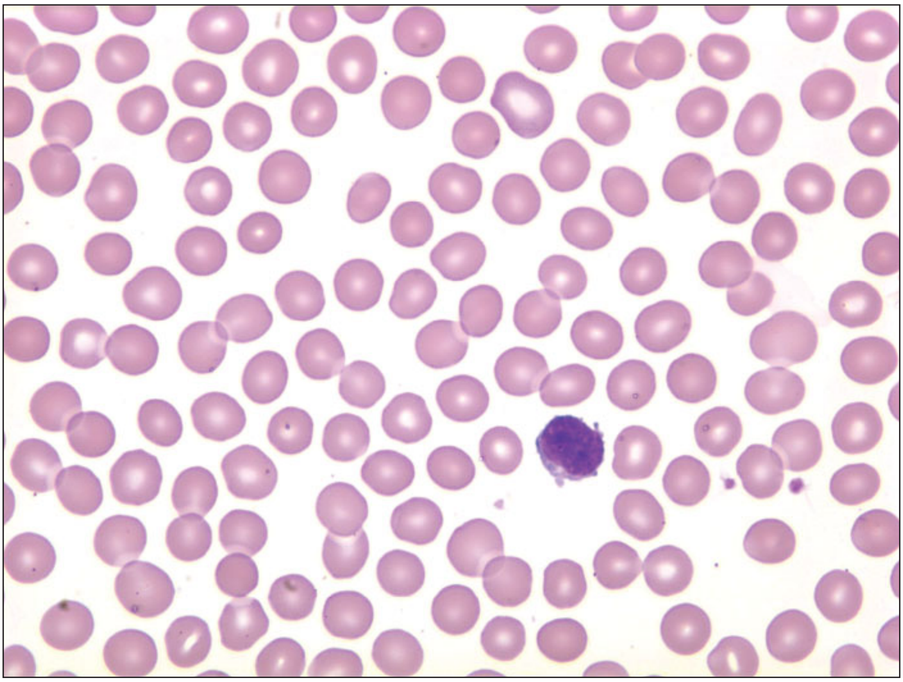


Figure IA1-7

Size: 7–7.5 µ

Nucleus

None

Cytoplasm

Color: Pink, central pallor about 1/3 of the cell
Contents: No mitochondria

MEGALOBLASTIC MATURATION SERIES

Megaloblastic Series

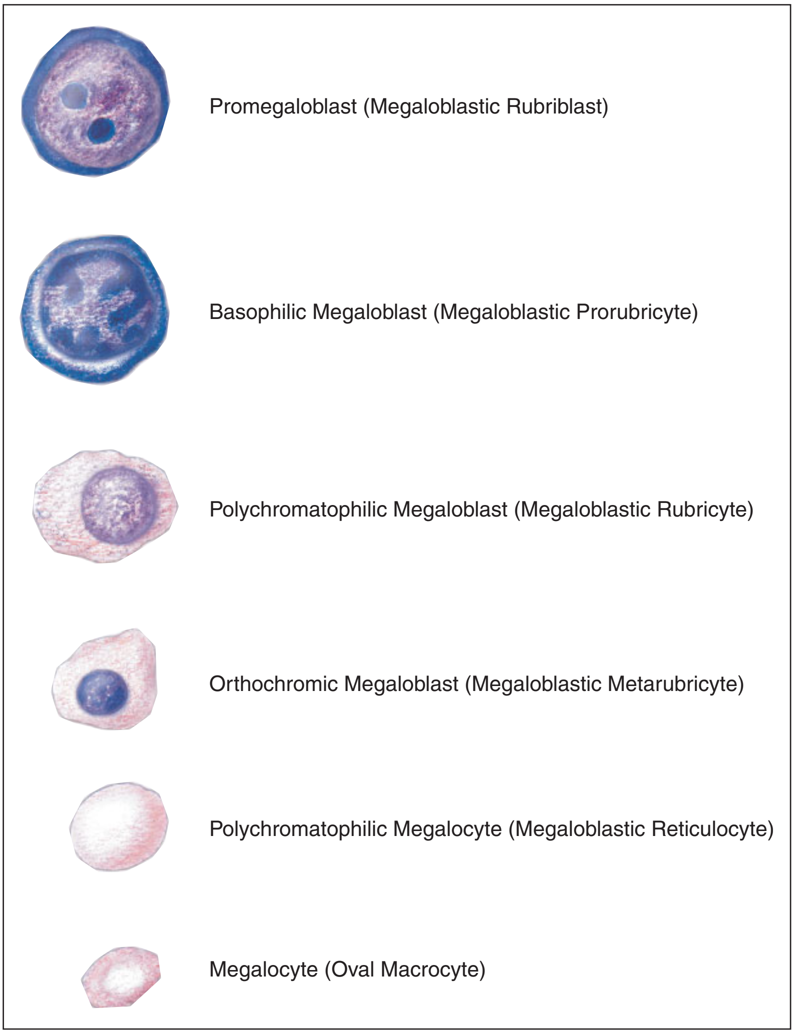

Promegaloblast (Megaloblastic Rubriblast)
Basophilic Megaloblast (Megaloblastic Prorubricyte)
Polychromatophilic Megaloblast (Megaloblastic Rubricyte)
Orthochromic Megaloblast (Megaloblastic Metarubricyte)
Polychromatophilic Megalocyte (Megaloblastic Reticulocyte)
Megalocyte (Oval Macrocyte)

Figure IA1-8

Promegaloblast (Megaloblastic Rubriblast)

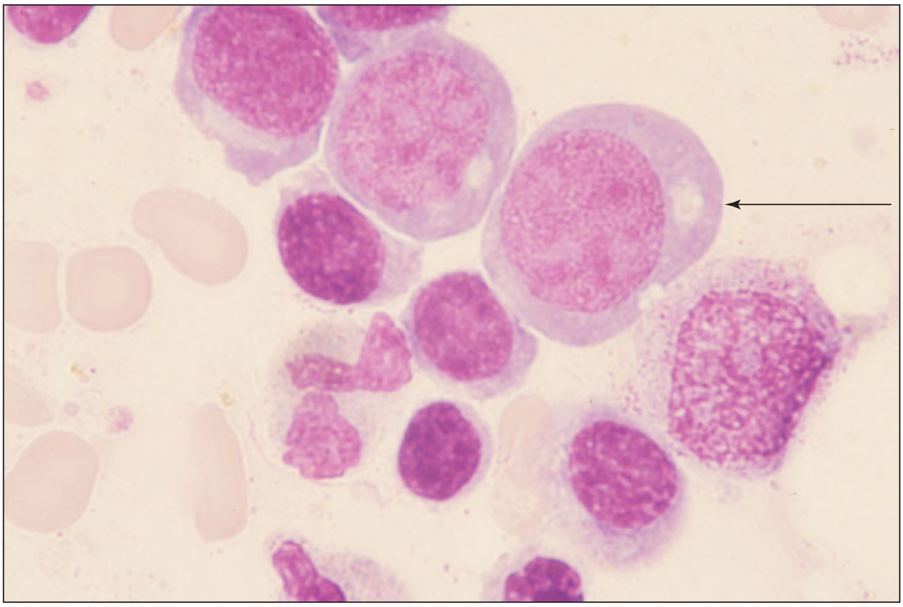


Figure IA1-9

Size: 19–27 μ

Nucleus

Shape: Round or irregular
N/C Ratio: 5:1
Color: Purple
Chromatin: Fine and closely meshed
Nucleoli: Multiple

Cytoplasm

Color: Deep blue
Contents: Nongranular with perinuclear halo

Clinical Conditions

- Vitamin B_{12} deficiency
- Folic acid deficiency
- Congenital dyserythropoietic anemia
- Erythroleukemia (FAB–M6a)
- Pure erythroid leukemia (FAB–M6b)
- Acute erythroid leukemia (WHO)

Basophilic Megaloblast (Megaloblastic Prorubricyte)

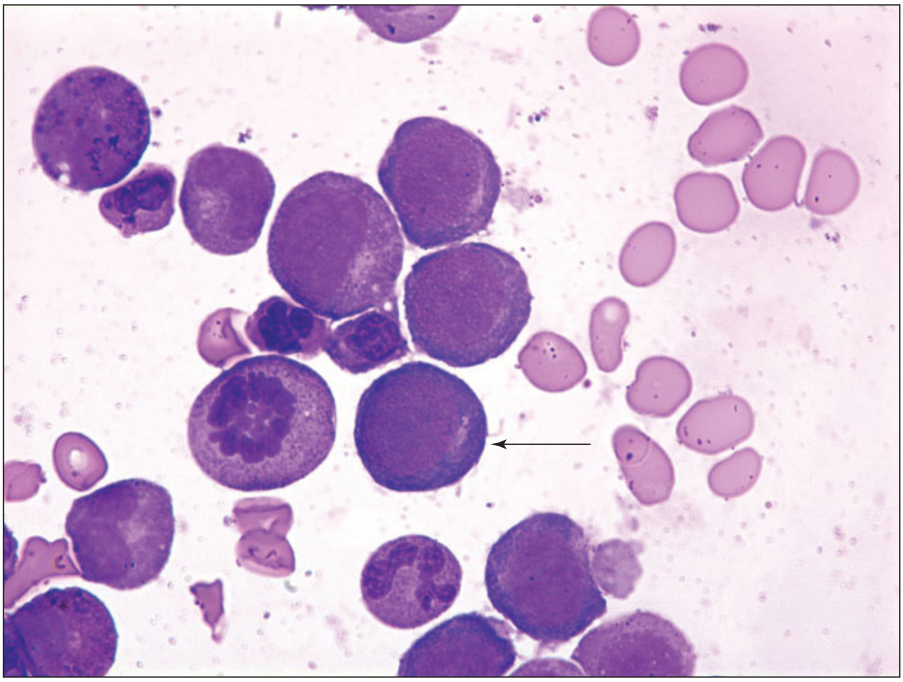


Figure IA1-10

Size: 17–24 μ

Nucleus

Shape: Round
N/C Ratio: 4:1
Color: Purple
Chromatin: Coarser than previous cell but still fine and open
Nucleoli: Not visible

Cytoplasm

Color: Deep blue
Contents: Faint perinuclear halo

Clinical Conditions

- Vitamin B_{12} deficiency
- Folic acid deficiency
- Congenital dyserythropoietic anemia
- Erythroleukemia (FAB–M6a)
- Pure erythroid leukemia (FAB–M6b)
- Acute erythroid leukemia (WHO)

Polychromatophilic Megaloblast (Megaloblastic Rubricyte)

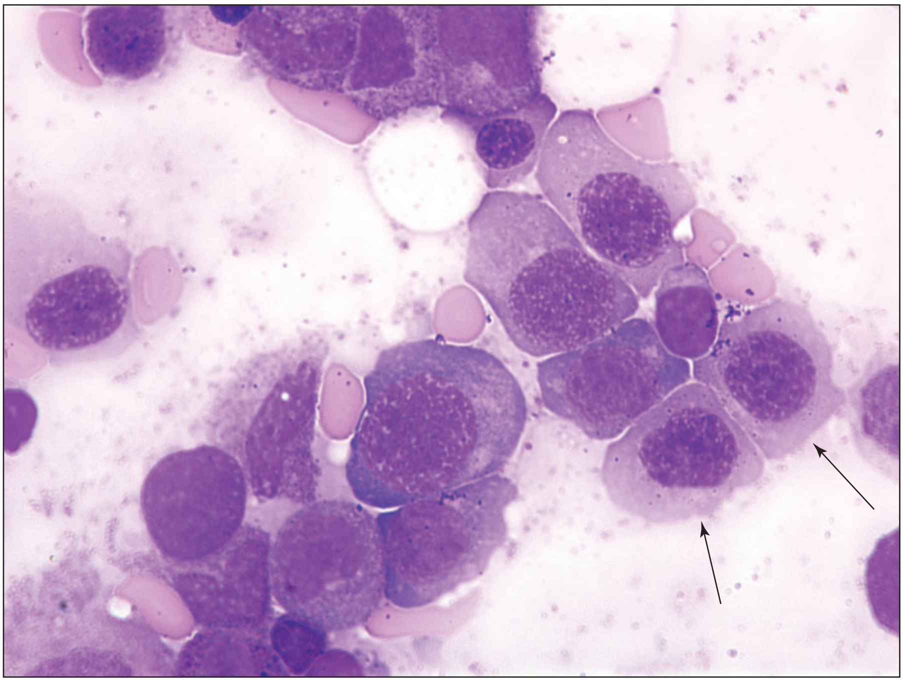


Figure IA1-11

Size: 15–20 µ

Nucleus

Shape: Round and central
N/C Ratio: 2:1
Color: Purple
Chromatin: Minimal clumping, loosely defined
Nucleoli: Not visible

Cytoplasm

Color: Blue-grey to pink-grey
Contents: More cytoplasm than in normoblastic cell

Clinical Conditions

- Vitamin B_{12} deficiency
- Folic acid deficiency
- Congenital dyserythropoietic anemia
- Erythroleukemia (FAB–M6a)
- Pure erythroid leukemia (FAB–M6b)
- Acute erythroid leukemia (WHO)

Orthochromic Megaloblast (Megaloblastic Metarubricyte)

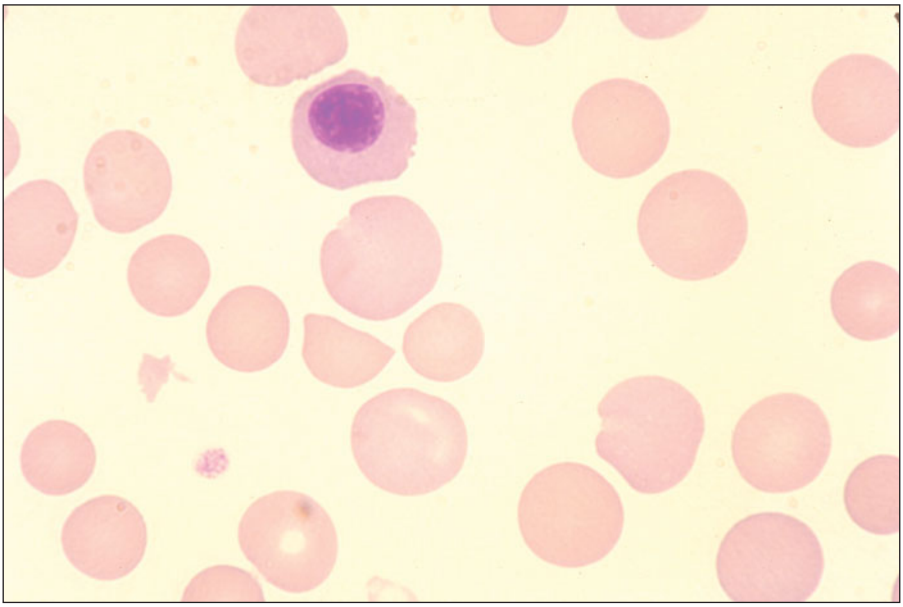


Figure IA1-12

Size: 10–15 μ

Nucleus

Shape: Round to slightly irregular, central or slightly eccentric
N/C Ratio: 1:1
Color: Deep purple but still some chromatin structure
Chromatin: Clumped, but less than in normoblastic cell
Nucleoli: Not visible

Cytoplasm

Color: Pink, with a hint of blue
Contents: More cytoplasm than in normoblastic cell

Clinical Conditions

- Vitamin B_{12} deficiency
- Folic acid deficiency
- Congenital dyserythropoietic anemia
- Erythroleukemia (FAB–M6a)
- Pure erythroid leukemia (FAB–M6b)
- Acute erythroid leukemia (WHO)

Polychromatophilic Megalocyte (Megaloblastic Reticulocyte)

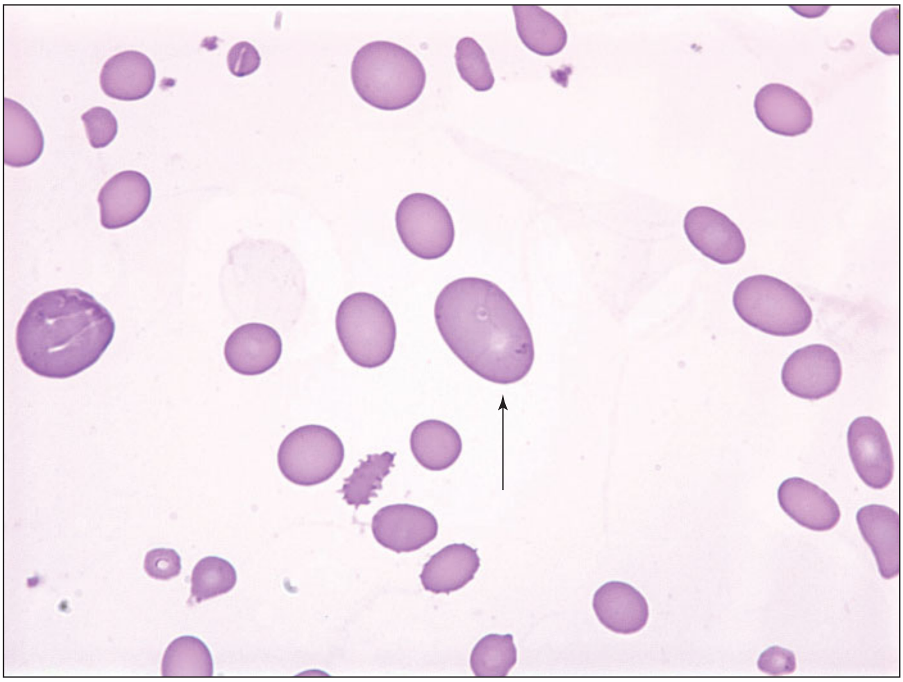


Figure IA1-13

Size: 9–15 µ

Nucleus

None

Cytoplasm

Color: Pink, with a hint of blue

Clinical Conditions

- Vitamin B_{12} deficiency
- Folic acid deficiency
- Congenital dyserythropoietic anemia
- Erythroleukemia (FAB–M6a)
- Pure erythroid leukemia (FAB–M6b)
- Acute erythroid leukemia (WHO)

Megalocyte (Oval Macrocyte)

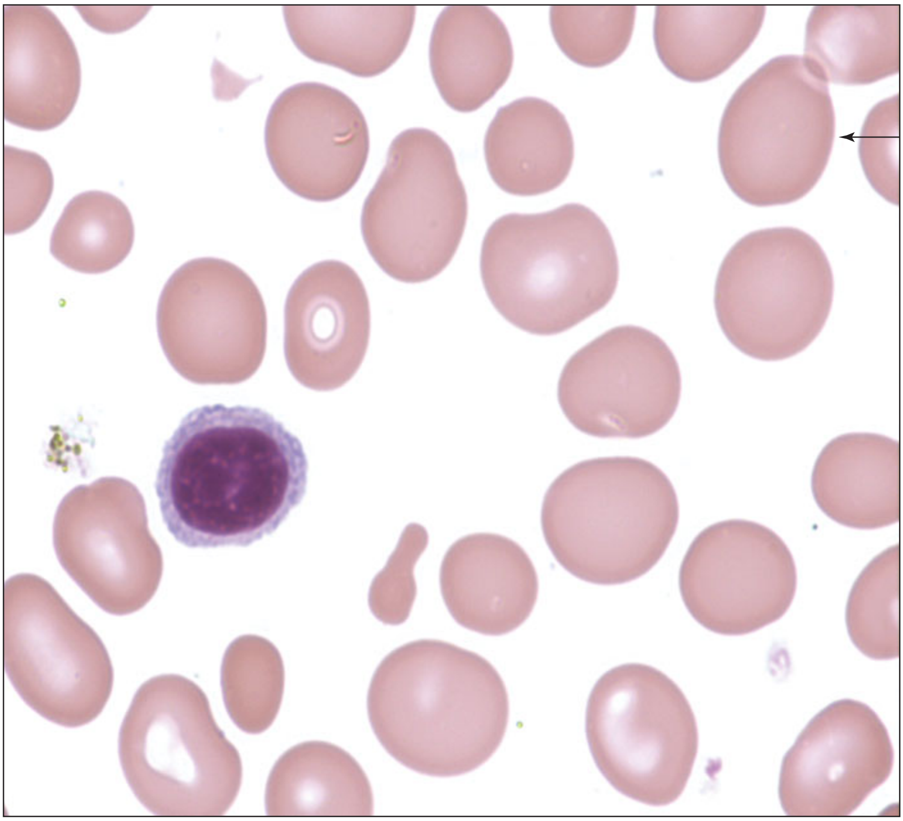


Figure IA1-14

Size: 9–12 µ

Nucleus

None

Cytoplasm

Color: Pink, central pallor less distinct
Contents: Increased hemoglobin content

Clinical Conditions

- Vitamin B_{12} deficiency
- Folic acid deficiency
- Congenital dyserythropoietic anemia
- Myelodysplastic syndromes
- Newborn
- Erythroleukemia (FAB–M6a)
- Pure erythroid leukemia (FAB–M6b)
- Acute erythroid leukemia (WHO)

IRON-DEFICIENT MATURATION SERIES

Iron-Deficient Series

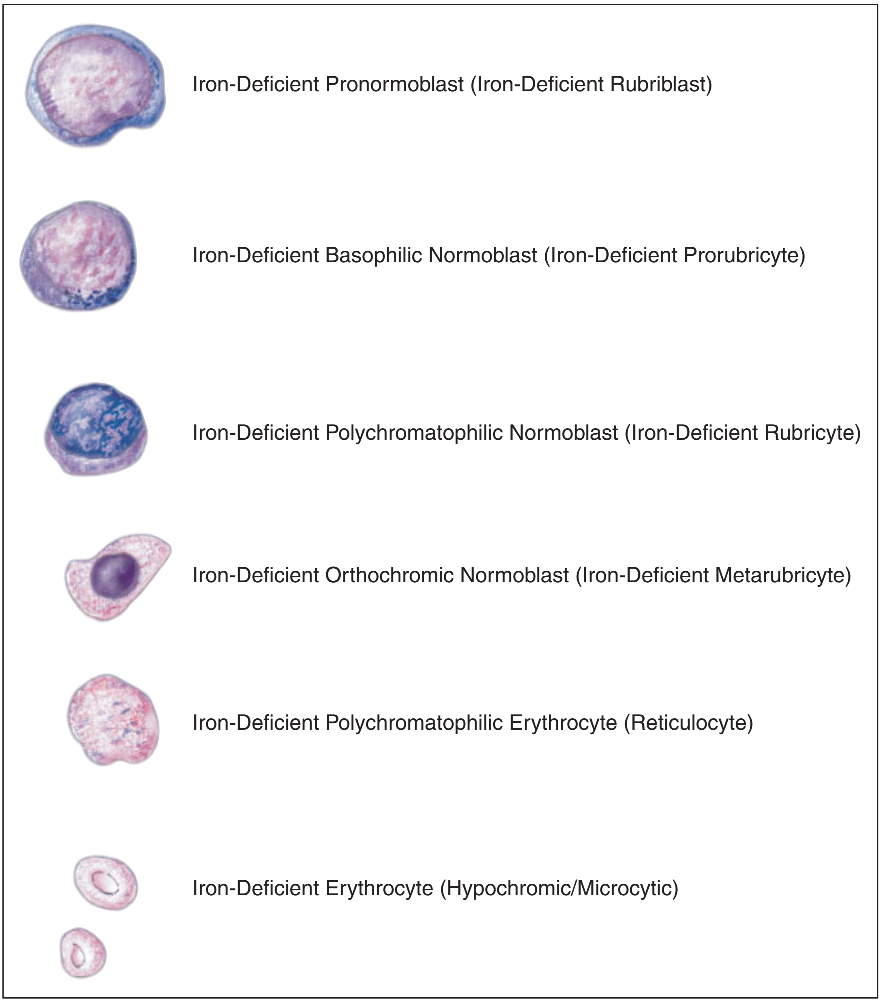

Iron-Deficient Pronormoblast (Iron-Deficient Rubriblast)
Iron-Deficient Basophilic Normoblast (Iron-Deficient Prorubricyte)
Iron-Deficient Polychromatophilic Normoblast (Iron-Deficient Rubricyte)
Iron-Deficient Orthochromic Normoblast (Iron-Deficient Metarubricyte)
Iron-Deficient Polychromatophilic Erythrocyte (Reticulocyte)
Iron-Deficient Erythrocyte (Hypochromic/Microcytic)

Figure IA1-15

Iron-Deficient Pronormoblast (Iron-Deficient Rubriblast)

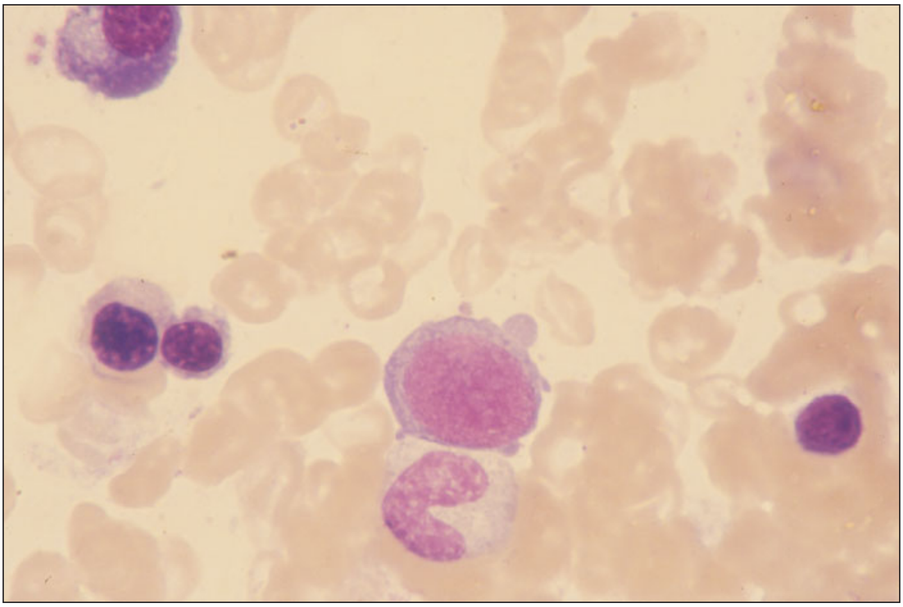


Figure IA1-16

Size: 14–20 µ

Nucleus

Shape: Irregularly round to slightly oval
N/C Ratio: 5:1
Color: Purple-red
Chromatin: Fine, but granular
Nucleoli: Present, but not distinct

Cytoplasm

Shape: Irregular
Color: Deep blue
Contents: Golgi; mitochondria, which produce a lighter blue perinuclear halo

Clinical Conditions

- Iron deficiency

Iron-Deficient Basophilic Normoblast (Iron-Deficient Prorubricyte)

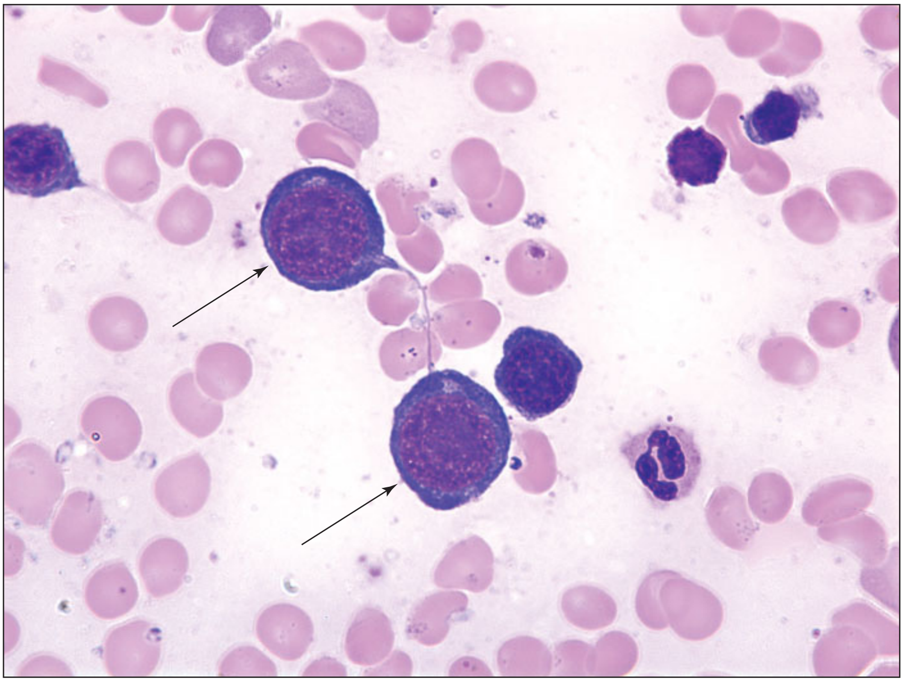


Figure IA1-17

Size: 10–15 µ

Nucleus

Shape: Round, centered
N/C Ratio: 5:1
Color: Purple, interspersed with light areas
Chromatin: Granular to slightly lumpy
Nucleoli: Usually not visible

Cytoplasm

Shape: Irregular
Color: Deep blue
Contents: Golgi may produce a light blue area near the nucleus; many mitochondria

Clinical Conditions

- Iron deficiency

Iron-Deficient Polychromatophilic Normoblast (Iron-Deficient Rubricyte)

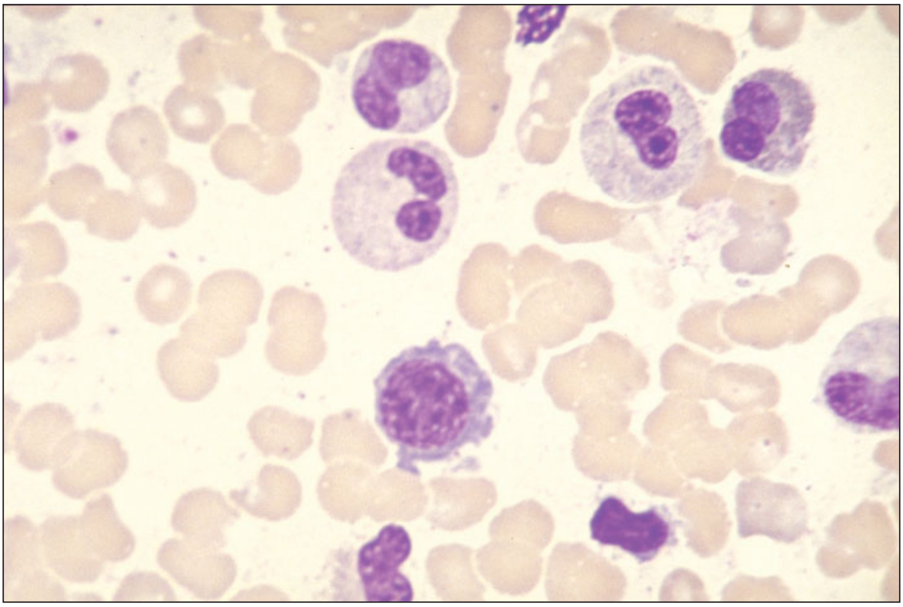


Figure IA1-18

Size: 9–12 μ

Nucleus

Shape: Round
N/C Ratio: 2:1
Color: Purple-red
Chromatin: Lumpy, with lighter parachromatin
Nucleoli: None

Cytoplasm

Color: Bluer than in normoblastic maturation
Contents: Lesser amount with shaggy blunt extensions

Clinical Conditions

- Iron deficiency

Iron-Deficient Orthochromic Normoblast (Iron-Deficient Metarubricyte)

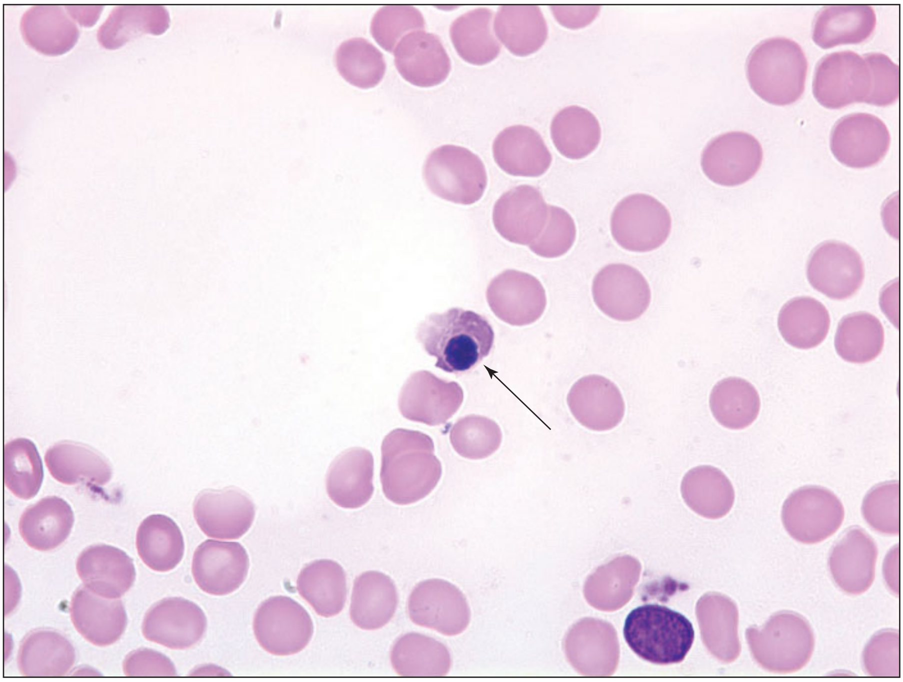


Figure IA1-19

Size: 7–11 µ

Nucleus

Shape: Round
N/C Ratio: 1:2
Color: Blue-purple
Chromatin: Condensed and homogeneous
Nucleoli: None

Cytoplasm

Shape: Irregular
Color: Pink, with residual blueness of RNA

Clinical Conditions

- Iron deficiency

Iron-Deficient Polychromatophilic Erythrocyte (Reticulocyte)

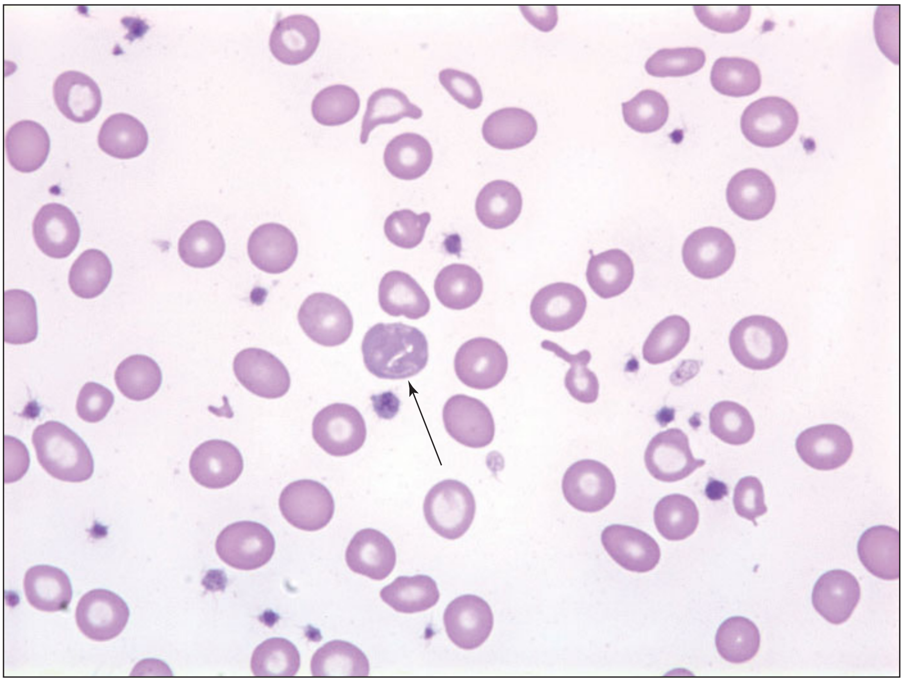


Figure IA1-20

Size: <6.5–10 μ

Nucleus

None

Cytoplasm

Color: Pink, with a hint of blue

Clinical Conditions

- Iron deficiency

Iron-Deficient Erythrocyte (Hypochromic/Microcytic)

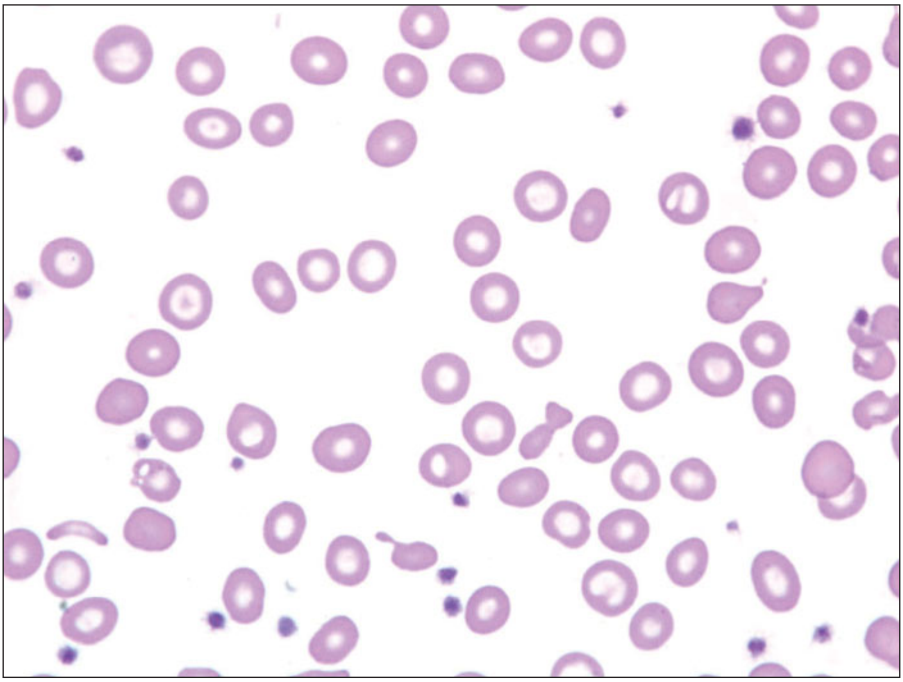


Figure IA1-21

Size: <6.5 μ

Nucleus

None

Cytoplasm

Color: Pink, central pallor greater than one-third of cell
Contents: Hemoglobin decreased

Clinical Conditions

- Iron deficiency

DISTRIBUTION

Agglutination

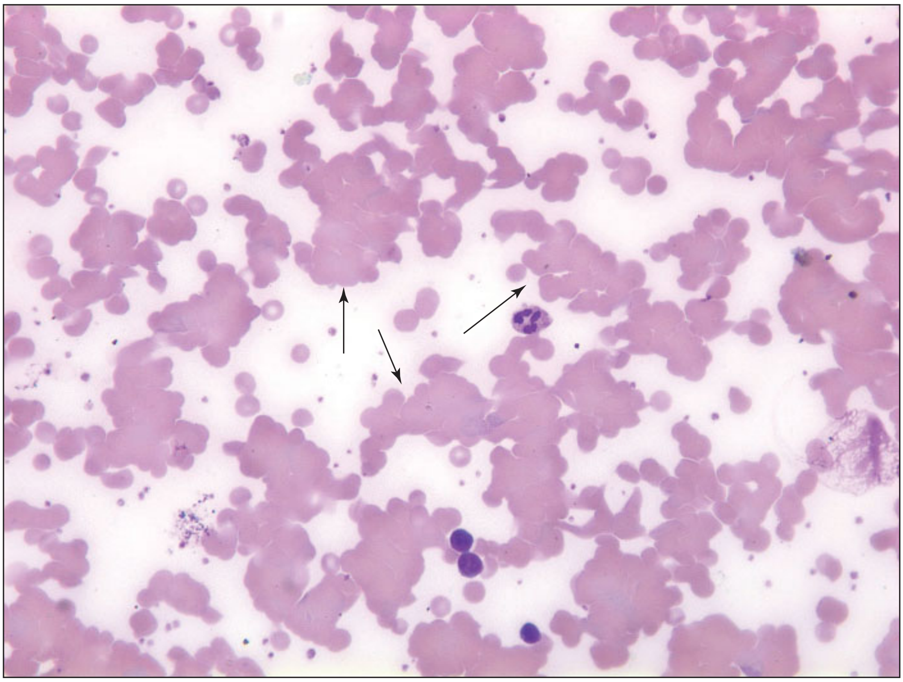


Figure IA1-22

Cell Type

Mature red blood cells

Description

Random masses or clusters of cells

Clinical Conditions

- Exposure to a variety of antibodies
- Hemolytic anemia (autoimmune)
- Atypical pneumonia
- Staphylococcal infections
- Trypanosomiasis
- Cold agglutinin disease

Rouleaux

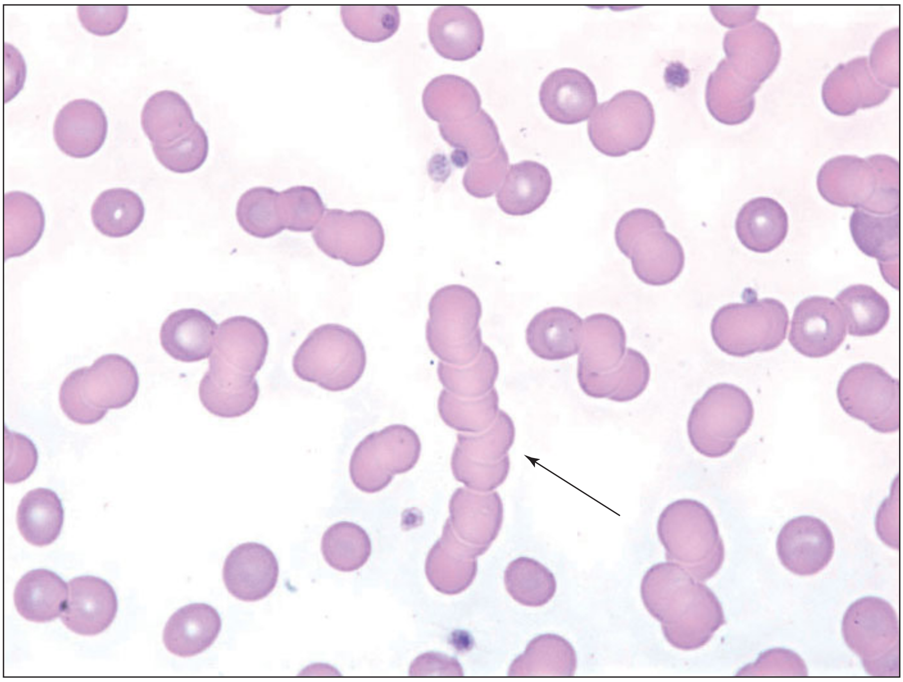


Figure IA1-23

Cell Type

Mature red blood cell

Description

Short or long stacks of cells (three or four or more) resembling coins; often a blue-staining background is also present

Clinical Conditions

- Hyperproteinemia
- Multiple myeloma
- Macroglobulinemia
- Increased fibrinogen (infection, pregnancy)

SHAPES

Acanthocyte

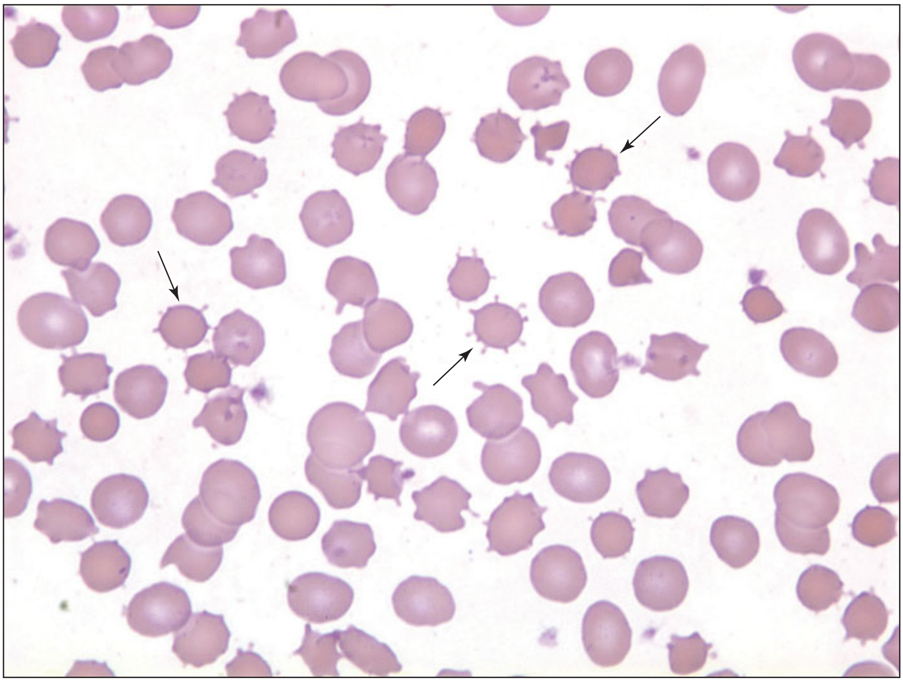


Figure IA1-24

Cell Type

Mature red blood cell

Description

Spherical and densely stained cell with 3–12 spicules of uneven length and width around the surface

Clinical Conditions

- Inherited lipid disorder (abetalipoproteinemia)
- Alcoholic cirrhosis
- Malabsorption states
- Neonatal hepatitis
- Pyruvate kinase deficiency

Codocyte (Target Cell)

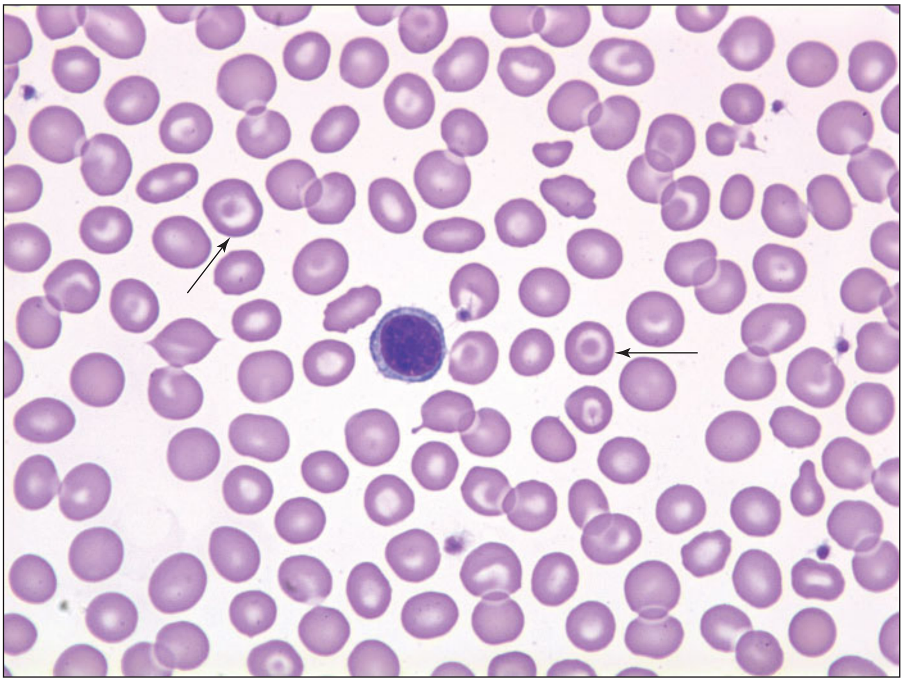


Figure IA1-25

Cell Type

Mature red blood cell

Description

Bell shaped, with a thin wall having a greater-than-normal surface membrane:volume ratio; central area of hemoglobin, a clear ring, and a peripheral ring of hemoglobin, giving an appearance of a bull's eye

Clinical Conditions

- Hemoglobinopathies
- Thalassemia
- Obstructive liver disease
- Iron deficiency anemia

Dacryocyte (Teardrop Cell)

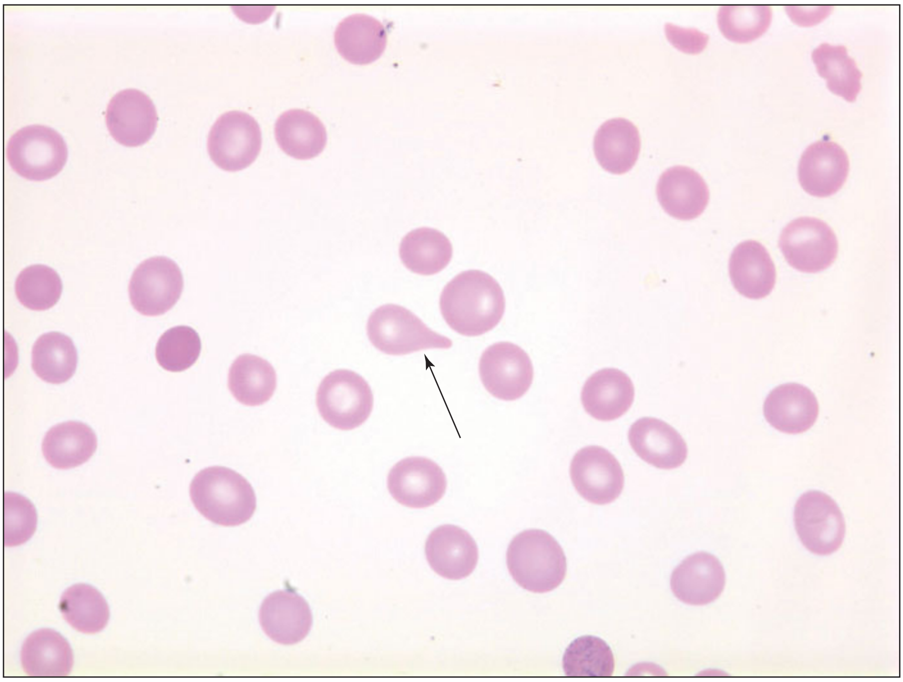


Figure **IA1-26**

Cell Type

Mature red blood cell

Description

Pear-shaped cell with a blunt pointed projection

Clinical Conditions

- Extramedullary hematopoiesis (myelofibrosis, myelophthisic anemia)
- Megaloblastic anemia
- Thalassemia
- Hypersplenism

Degmacyte (Bite Cell)

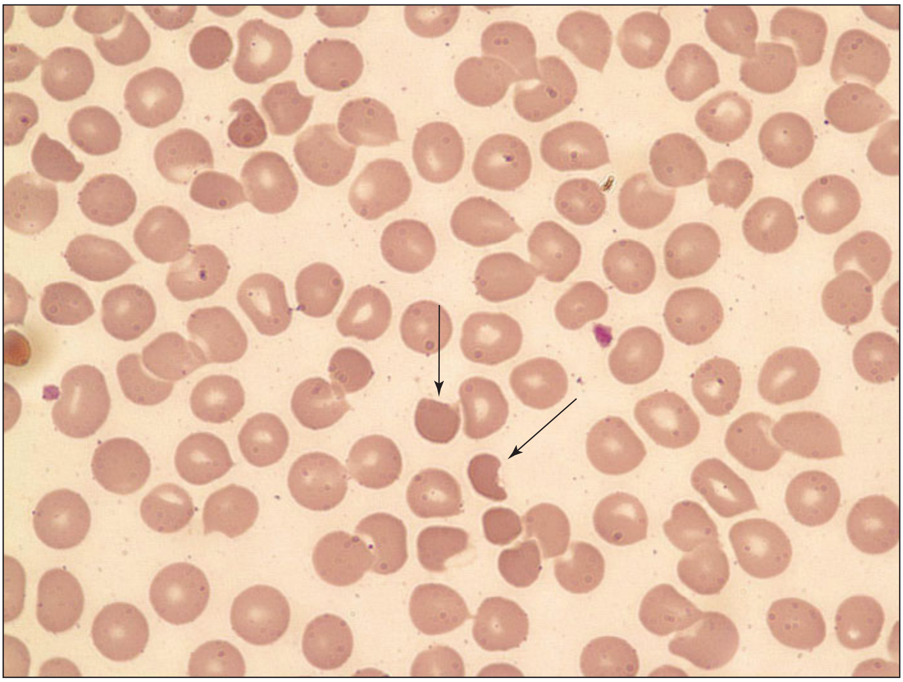


Figure IA1-27

Cell Type

Mature red blood cell

Description

Semicircular area (denatured and precipitated masses of hemoglobin) of cell removed by spleen; these cells may show multiple peripheral defects

Clinical Conditions

- Drug-induced anemias
- Glucose-6-phosphate dehydrogenase deficiency
- Thalassemia
- Unstable hemoglobinopathies

Drepanocyte (Sickle Cell)

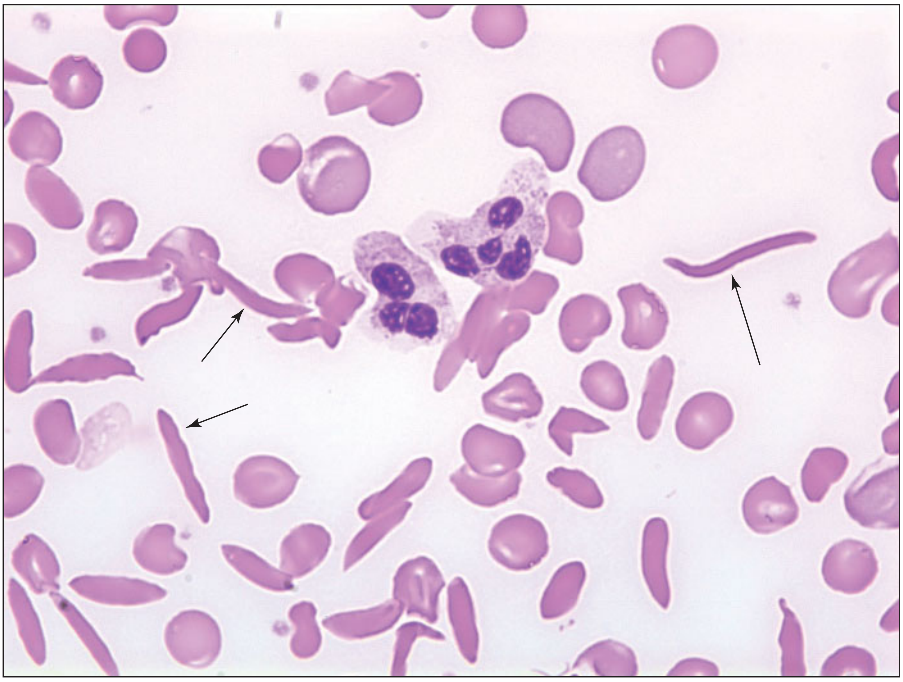


Figure IA1-28

Cell Type

Mature red blood cell

Description

Elongated cell due to polymers of abnormal hemoglobin; terminal projections, causing the cell to take on an irregular shape; usually lacks a central pallor

Clinical Conditions

- Hemoglobinopathies (SS, SC, SD, S-β thalassemia)

Echinocyte (Burr Cell)

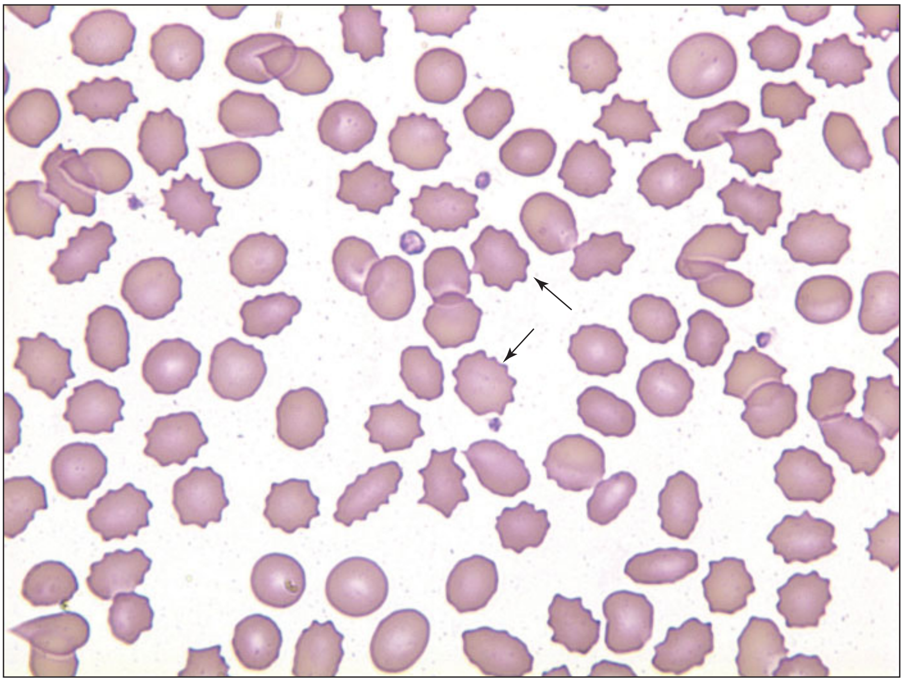


Figure **IA1-29**

Cell Type

Mature red blood cell

Description

Cell with evenly distributed, short spicules; the spicules have a blunt end; retains central pallor

Clinical Conditions

- Slow drying in high humidity
- Renal insufficiency
- Pyruvate kinase deficiency
- Stored blood
- Severe dehydration
- Burns

Keratocyte (Horn Cell)

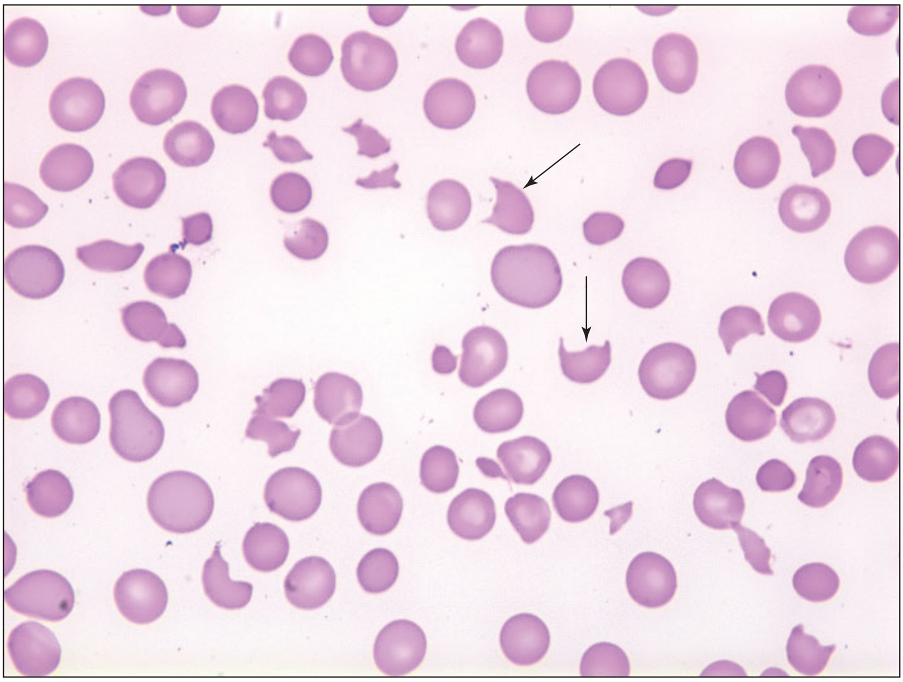


Figure IA1-30

Cell Type

Mature red blood cell

Description

Cell with projections (usually two) that resemble horns

Clinical Conditions

- Microangiopathic hemolytic anemia
- Glomerulonephritis
- Waring Blender syndrome
- Pyruvate kinase deficiency

Knizocyte (Pinch Cell)

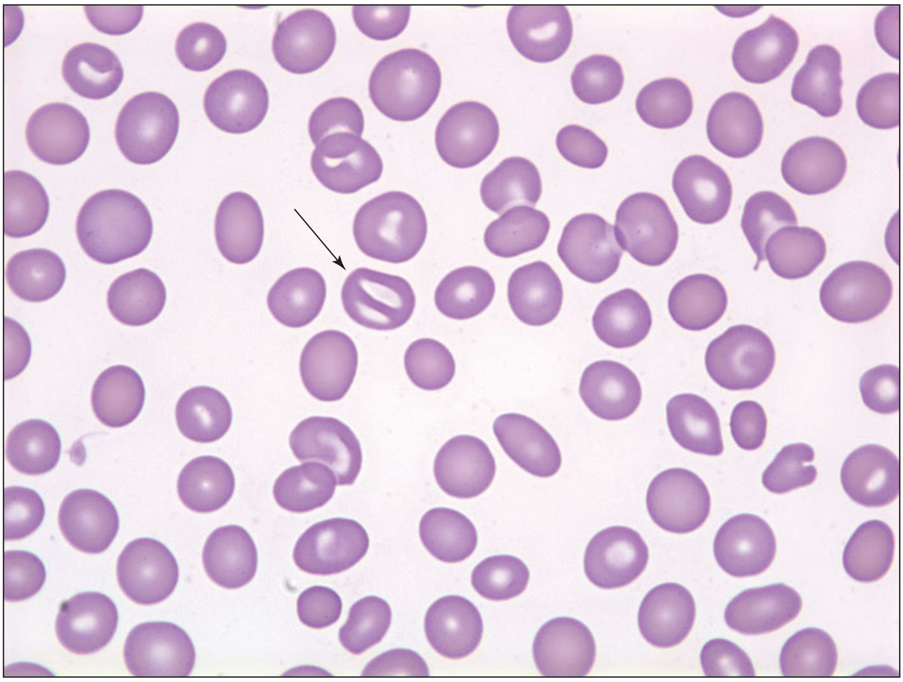


Figure IA1-31

Cell Type

Mature red blood cell

Description

Cell with triconcave shape having two central pallors

Clinical Conditions

- Hemolytic anemia
- Hemoglobinopathies
- Pancreatitis

Ovalocyte (Elliptocyte)

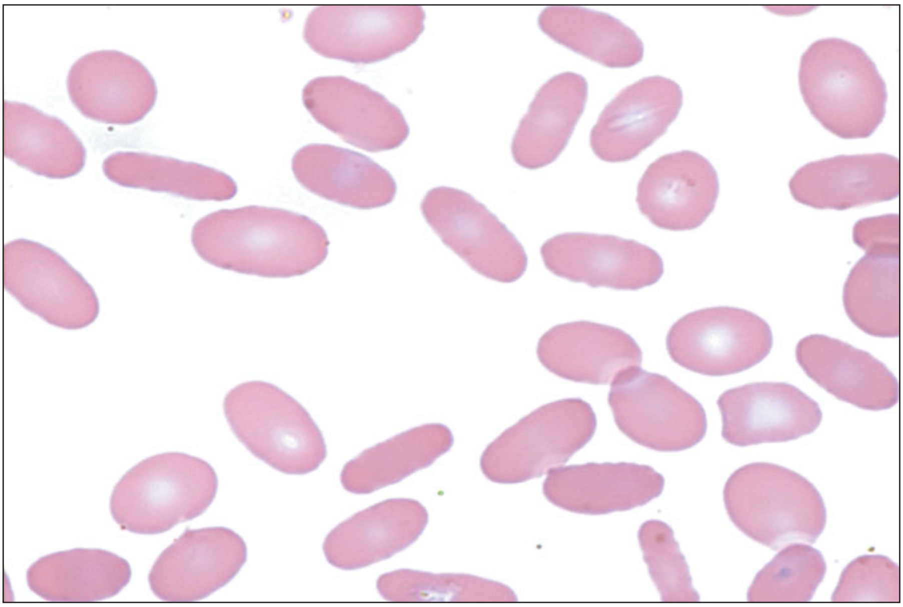


Figure IA1-32

Cell Type

Mature red blood cell

Description

Oval-shaped cell (may be slightly egg, rod, or pencil shaped); hemoglobin is concentrated at two ends; normal central pallor

Clinical Conditions

- Hereditary elliptocytosis
- Iron deficiency anemia
- Myelophthisic anemia
- Megaloblastic anemia
- Thalassemia
- Sideroblastic anemia
- Congenital dyserythropoietic anemia

Pyknocyte (Blister Cell)

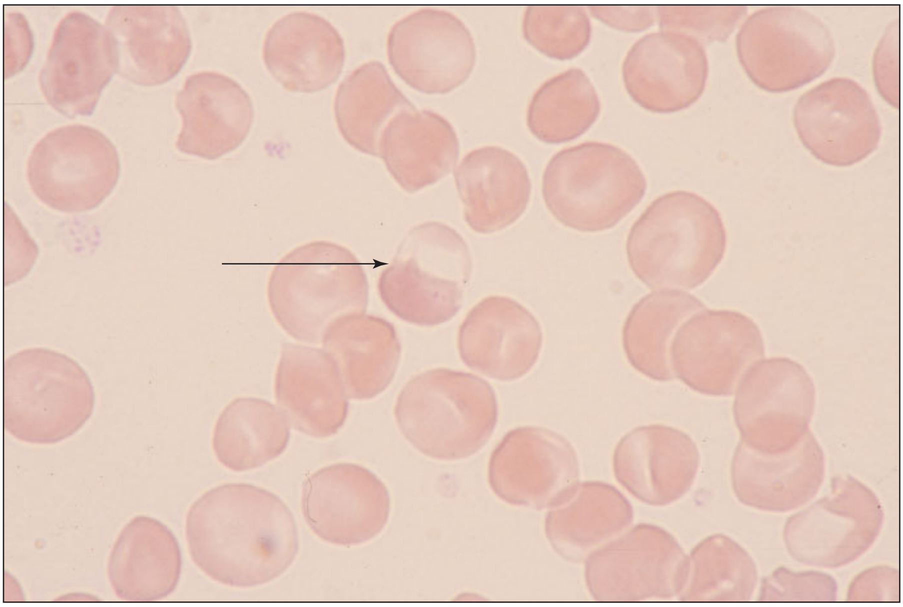


Figure IA1-33

Cell Type

Mature red blood cell

Description

Cell with a clearing on one side and a concentrated area of hemoglobin on the other side

Clinical Conditions

- Infantile pyknocytosis
- Infantile viremia

Schistocyte (Schizocyte)

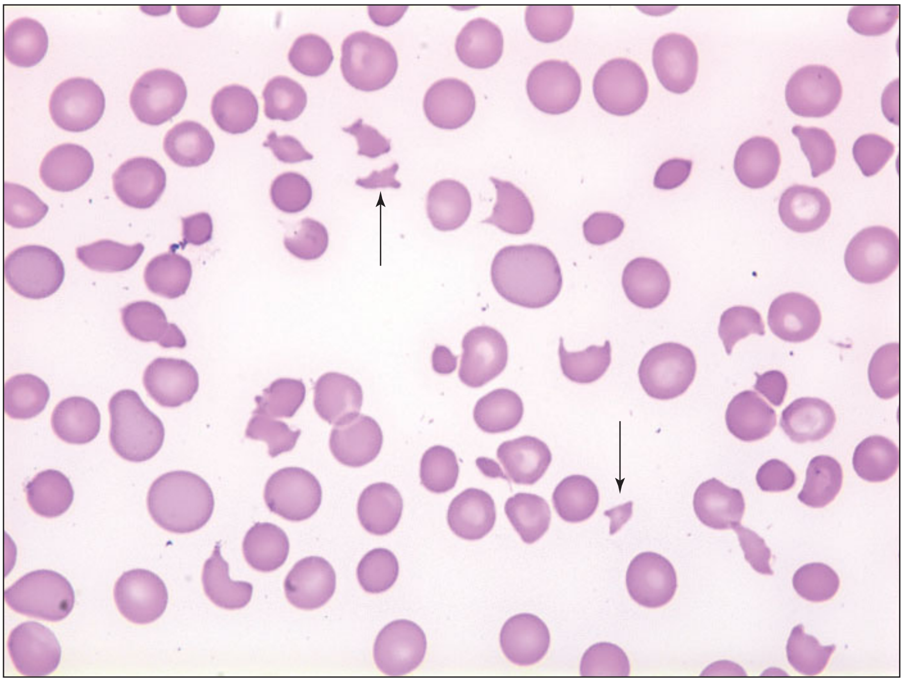


Figure IA1-34

Cell Type

Mature red blood cell

Description

Irregular shape or fragment of cell; results from damaged membrane

Clinical Conditions

- Microangiopathic hemolytic anemias
- Traumatic hemolytic anemias
- Waring Blender syndrome

Spherocyte

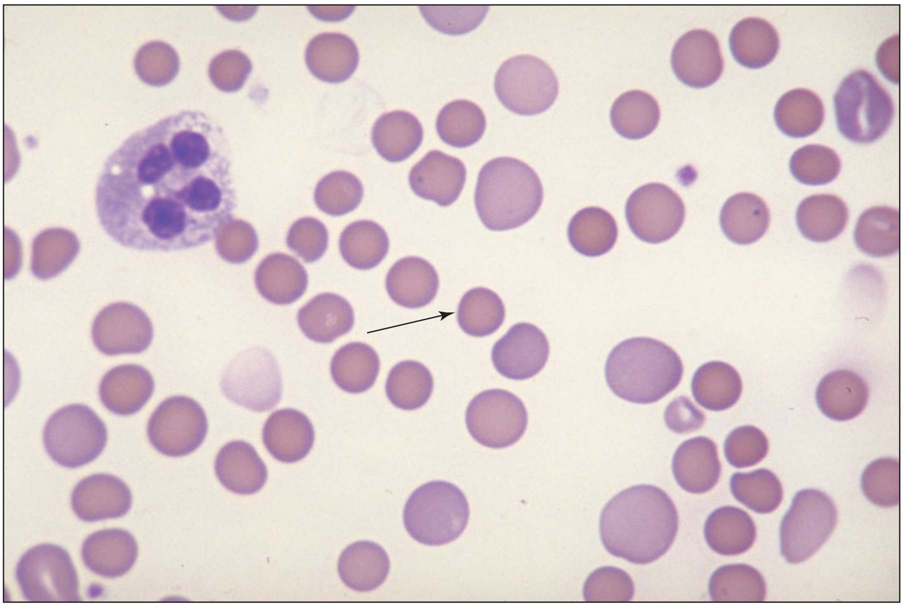


Figure **IA1-35**

Cell Type

Mature red blood cell

Size: 6.1–7.0 μ

Description

Round cells; increased staining intensity with no central pallor; smaller volume than a normal cell (decreased surface:volume ratio)

Clinical Conditions

- Hereditary spherocytosis
- Immunohemolytic anemias
- Heinz body hemolytic anemia
- Severe burns (microspherocytes seen); microspherocytes are <4.0 μ
- Hypersplenism

Stomatocyte

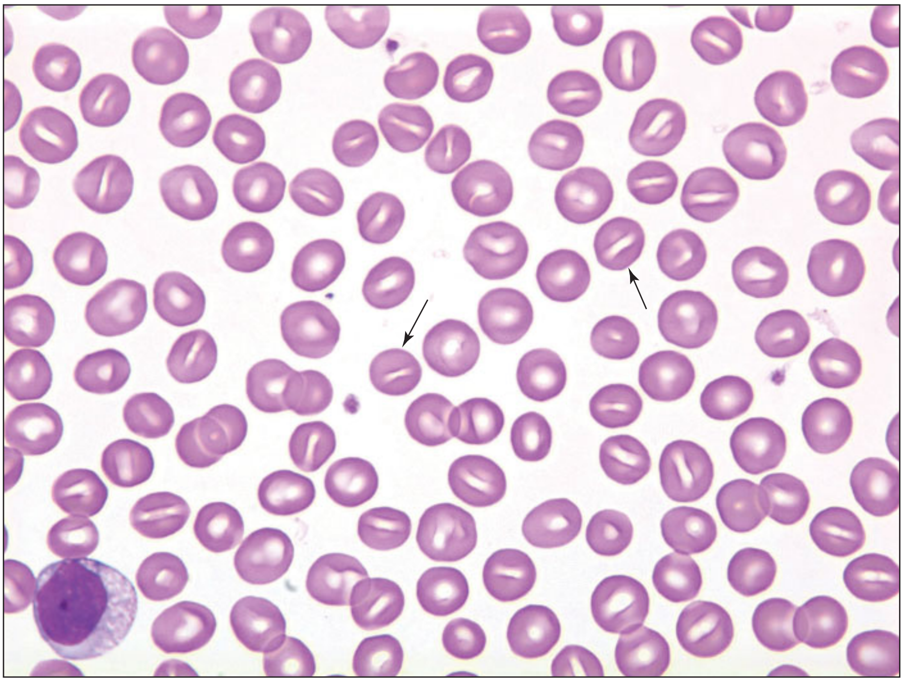


Figure IA1-36

Cell Type

Mature red blood cell

Description

Cell having a slitlike area of central pallor

Clinical Conditions

- Hereditary stomatocytosis
- Alcoholism
- Obstructive liver disease
- Cirrhosis
- Rh-null disease

SIZE

Macrocyte

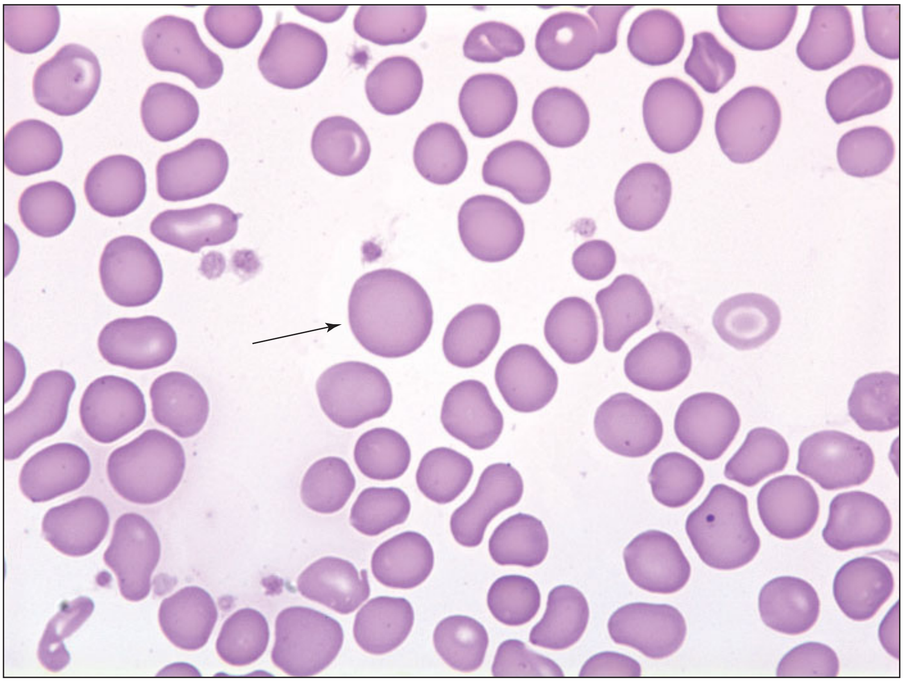


Figure **IA1-37**

Size: >7.8 µ

Cell Type

Mature red blood cell

Description

Large cell, mean corpuscular volume usually >100 fL; usually normochromic; may be round or oval; cytoplasm is pink-red

Clinical Conditions

- Liver disease (round macrocytes seen)
- Megaloblastic anemias (oval macrocytes seen)
- Myelodysplastic syndrome
- Acute blood loss
- Chemotherapy

Microcyte

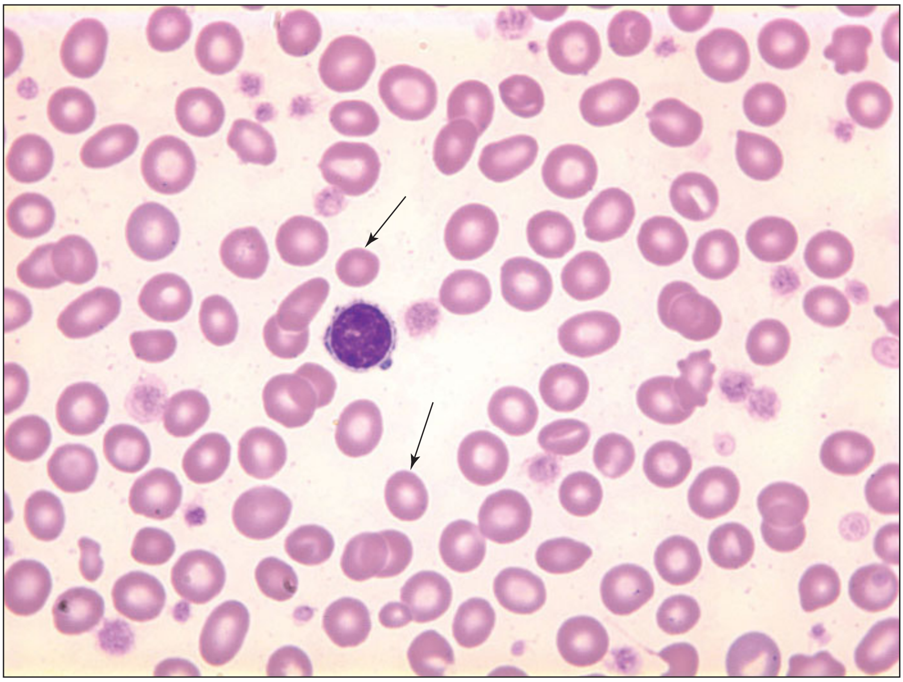


Figure IA1-38

Size: <6.5 µ

Cell Type

Mature red blood cell

Description

Smaller than a normal cell; mean corpuscular volume usually <80 fL; has a central pallor; normochromic or hypochromic

Clinical Conditions

- Iron deficiency anemia
- Thalassemias
- Lead poisoning
- Anemia of chronic disease
- Sideroblastic anemia

COLORING

Dimorphic

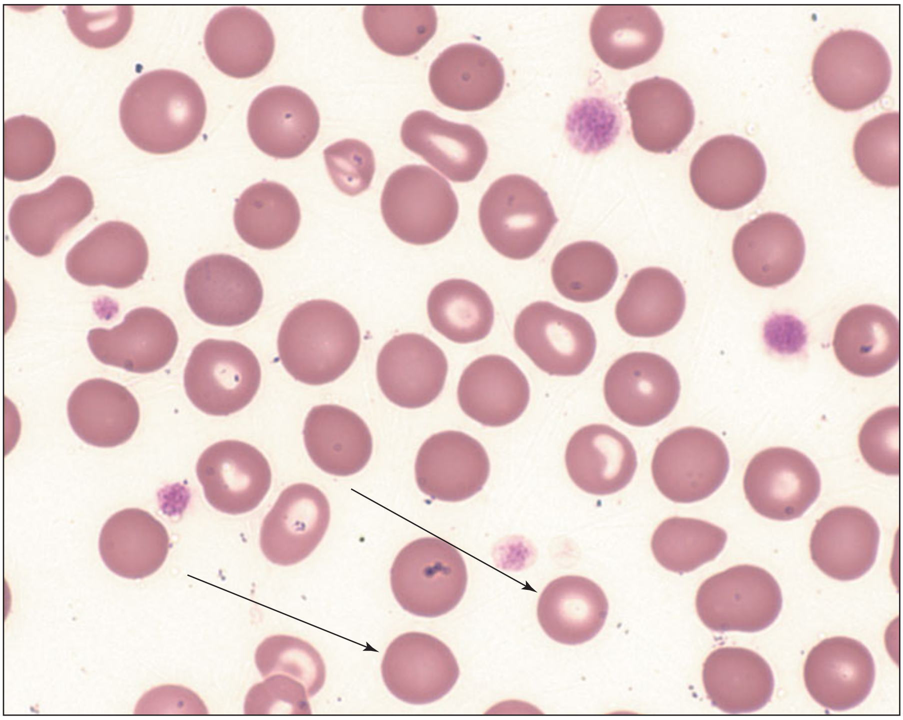


Figure IA1-39

Cell Type

Mature erythrocytes

Size: 6–11 μ

Description

Dual population of cells, normocytic and microcytic; normocytic and macrocytic; may also exhibit normochromia and hypochromia

Clinical Conditions

- Sideroblastic anemia
- Myelodysplastic syndromes

Hypochromic

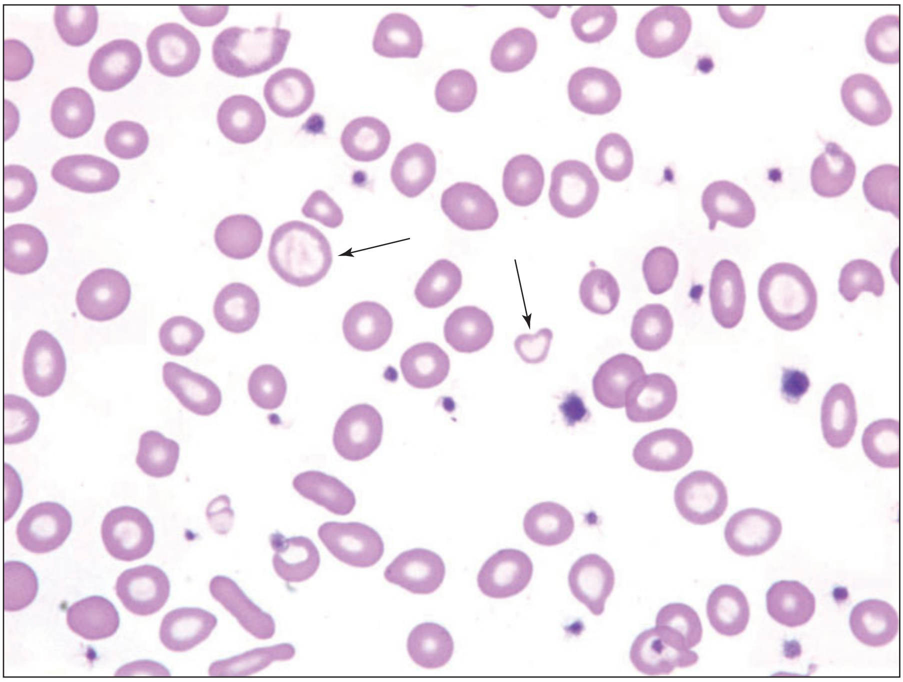


Figure IA1-40

Cell Type

Mature red blood cell

Description

Cells possess a greater central pallor than normal (greater than one-third); may lack hemoglobin and have a decreased mean corpuscular hemoglobin concentration or may be abnormally thin

Clinical Conditions

- Iron deficiency anemia
- Thalassemia
- Anemia of chronic disease
- Sideroblastic anemia
- Myelodysplastic syndromes

Polychromatophilic

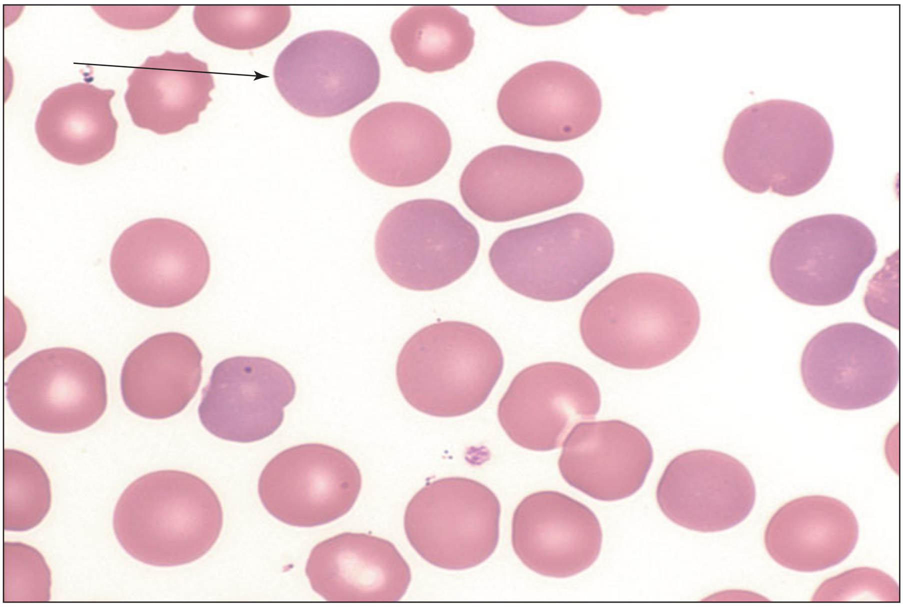


Figure IA1-41

Cell Type

Young red blood cell with no nucleus

Size: 8–11 μ

Description

Contains residual RNA, which stains diffusely blue; identified as reticulocyte when stained with a supravital dye

Clinical Conditions

- Increased erythrocyte production
- Hemolytic anemias
- Membrane disorders
- Hemolytic disease of the newborn

INCLUSIONS

Basophilic Stippling (Punctate Basophilia)

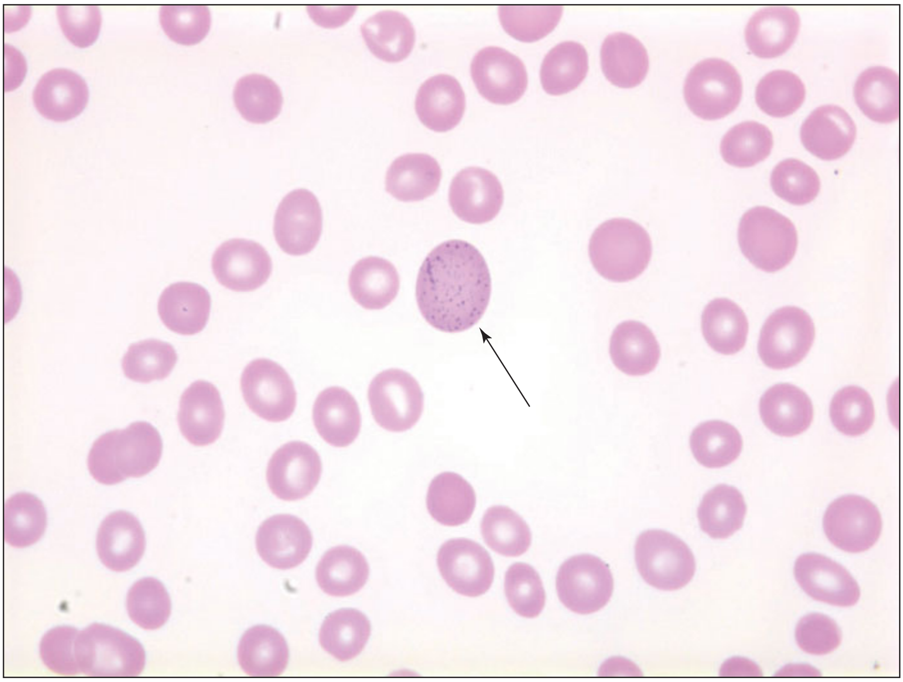


Figure IA1-42

Cell Type

Mature red blood cell

Description

Coarse, deep blue inclusions; irregularly aggregated or clumped ribosomes throughout the cell; mitochondria and siderosomes may also aggregate

Clinical Conditions

- Altered hemoglobin biosynthesis
- Lead intoxication
- Thalassemia
- Megaloblastic anemia
- Alcoholism
- Sideroblastic anemia
- Pyrimidine-5′-nucleotidase deficiency

Cabot Ring

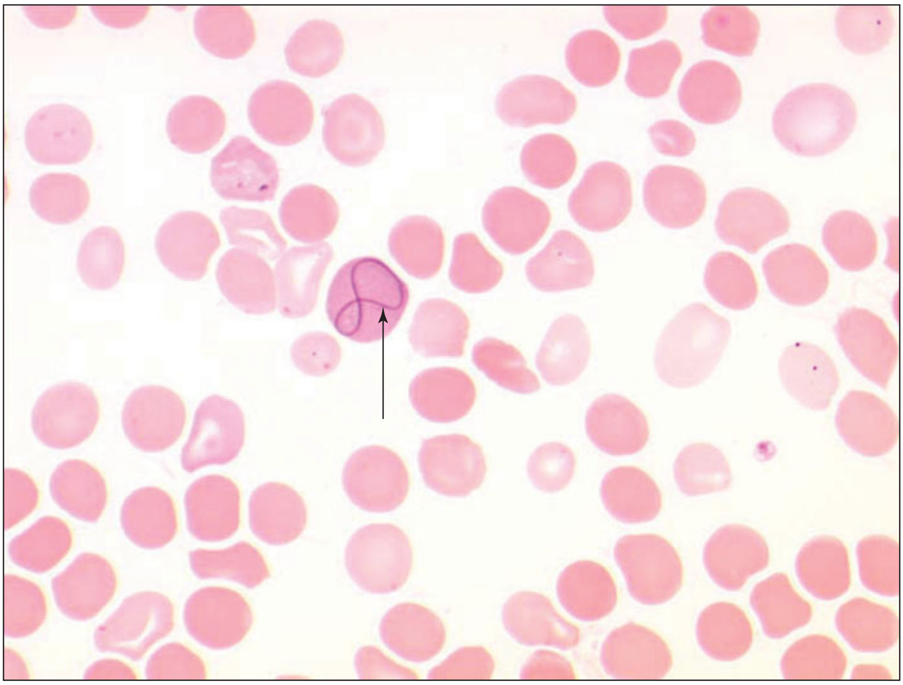


Figure IA1-43

Cell Type

Mature red blood cell

Description

Oval or figure eight–shaped inclusion; red-violet; usually one per cell; consists of nuclear remnants or part of the mitotic spindle

Clinical Conditions

- Severe anemias
- Dyserythropoiesis

Heinz Bodies

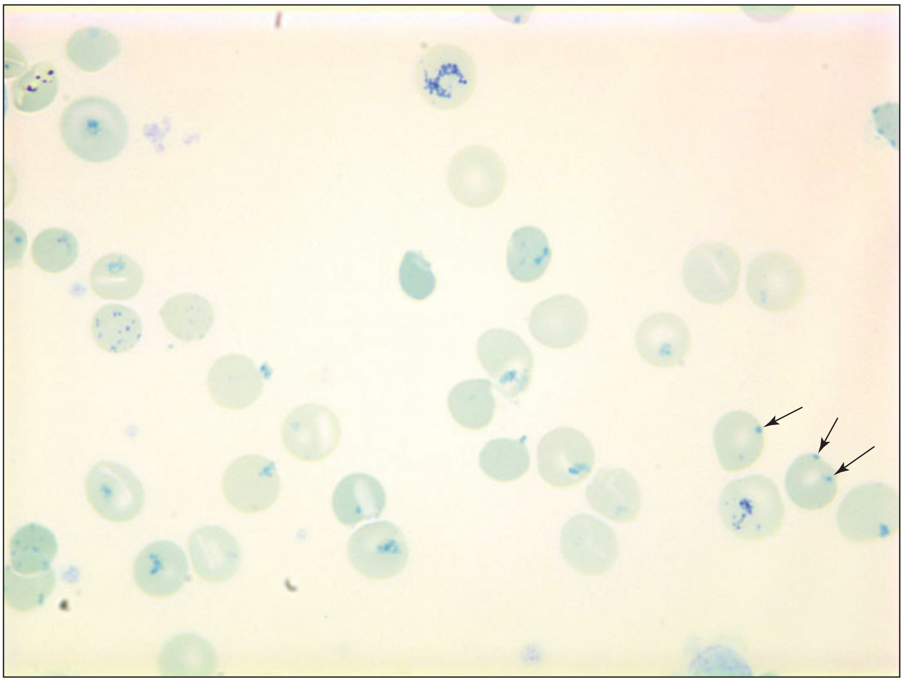


Figure **IA1-44**

Cell Type

Young and mature red blood cells

Size: 1–2 μ

Description

Round, refractile inclusions found on the periphery of the cell when stained with a supravital dye; consists of denatured globin produced by the destruction of hemoglobin; they may occur in multiple numbers

Clinical Conditions

- Drug-induced anemias
- Thalassemia
- Glucose-6-phosphate dehydrogenase deficiency and other red blood cell enzymopathies
- Unstable hemoglobinopathies

Hemoglobin C Crystals

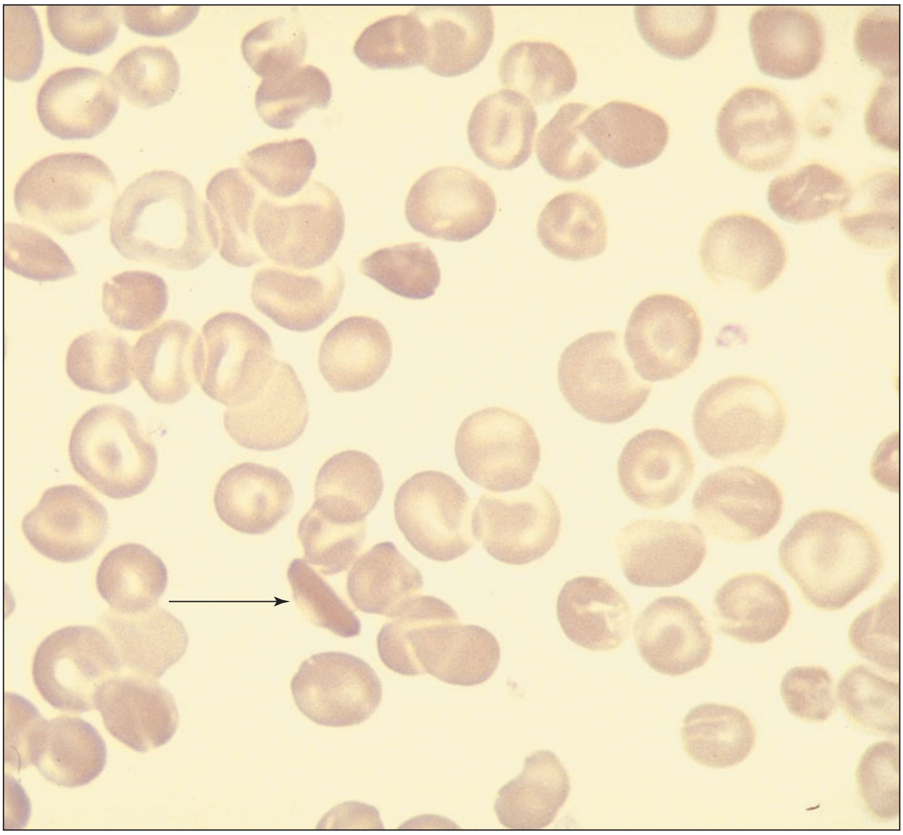


Figure IA1-45

Cell Type

Mature red blood cells

Description

Hexagonal, rod-shaped inclusions with blunt ends that stain very dark; formed within the cell membrane; remainder of cell has a clear area

Clinical Condition

- Hemoglobin CC disease

Hemoglobin H Inclusions

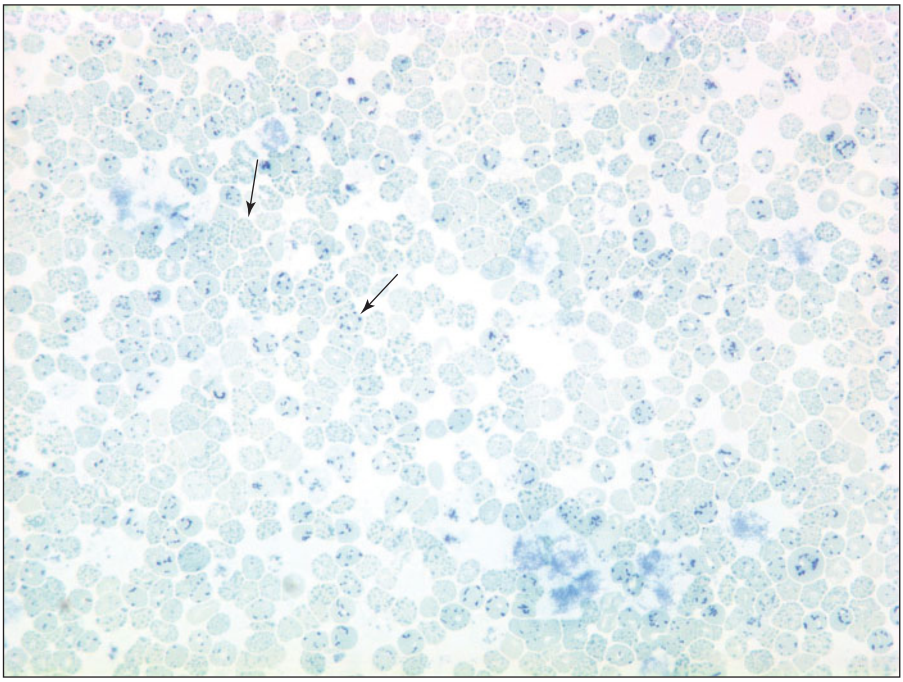


Figure IA1-46

Cell Type

Nucleated and nonnucleated red blood cells

Description

Unpaired beta-chains form small, greenish-blue inclusions when stained with brilliant cresyl blue; uniformly dispersed throughout the cell; when present in multiple numbers, they give the cell a “golf ball” appearance

Clinical Condition

- Hemoglobin H disease

Hemoglobin SC Crystals

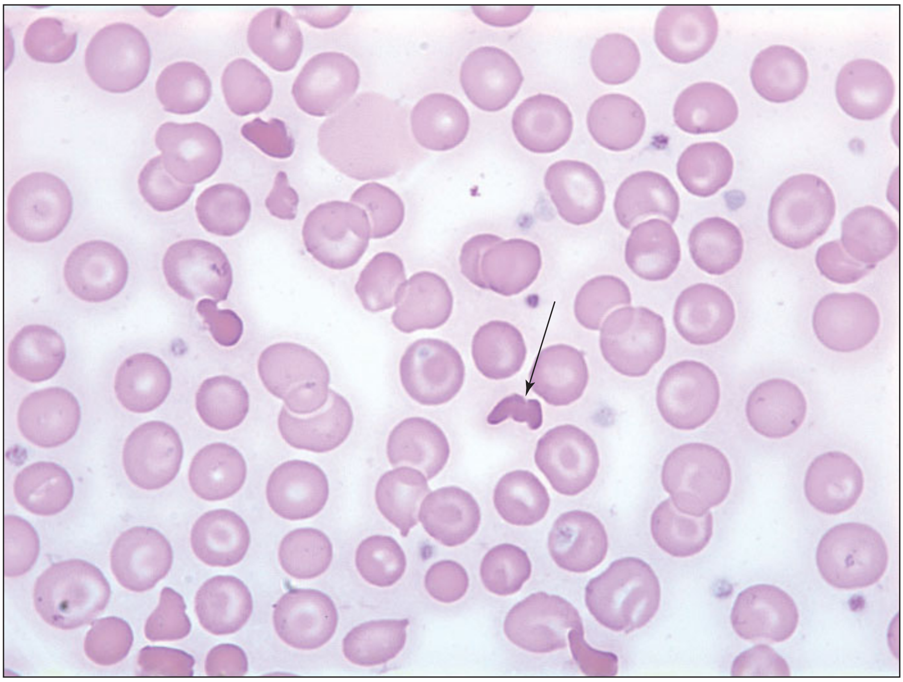


Figure IA1-47

Cell Type

Mature red blood cell

Description

Darkly stained condensed hemoglobin; crystals may be straight with parallel sides and a blunt protruding end or have several fingerlike projections from the center; crystals may protrude from the cell membrane; remainder of cell has pallor or distorted membrane

Clinical Condition

- Hemoglobin SC disease

Howell-Jolly Body

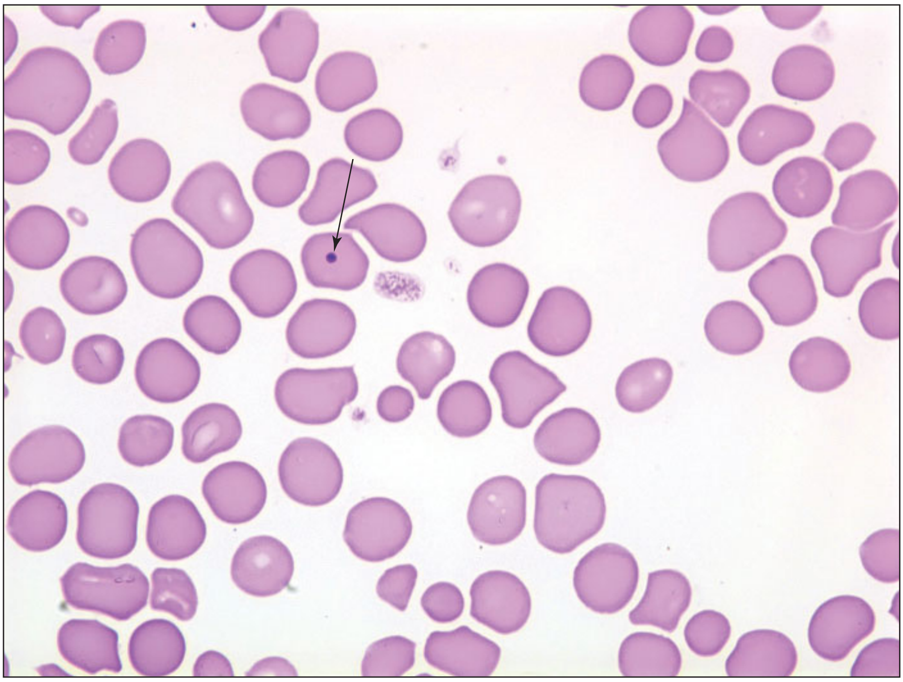


Figure IA1-48

Size: 0.5–1.0 µ

Cell Type

Nucleated and nonnucleated red blood cells

Description

Round fragments of nucleus (DNA); reddish-blue to deep purple; usually one per cell but occasionally may be two or more; represents chromosomes that have been separated from the mitotic spindle during abnormal mitosis; may also appear to arise from nuclear fragmentation or abnormal expulsion of the nucleus

Clinical Conditions

- Megaloblastic anemia
- Hemolytic anemias
- Hyposplenism
- Splenectomized persons
- Alcoholism
- Sickle cell anemia

Malaria

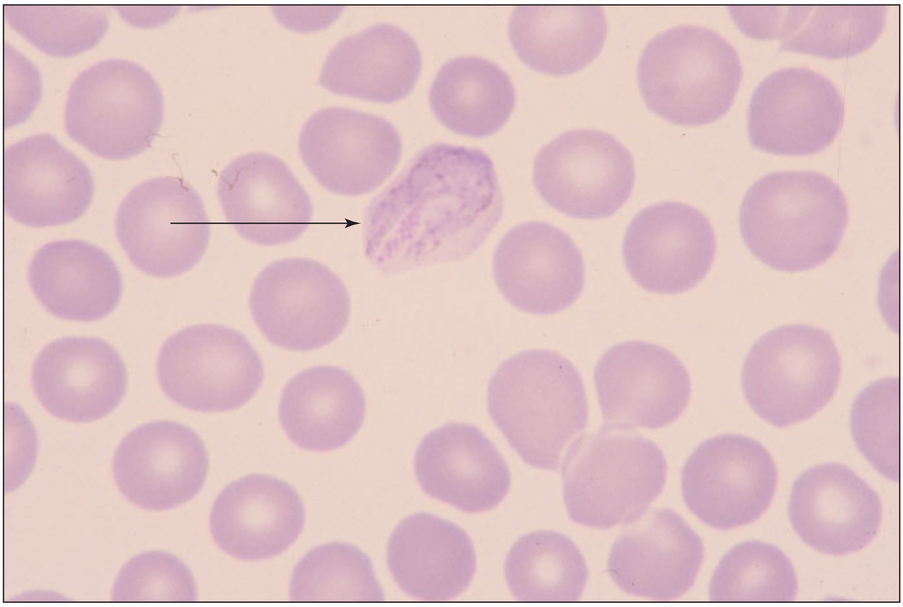


Figure IA1-49

Cell Type

Red blood cell

Description

Depends on the species of *Plasmodium* that infects the cells:

Plasmodium vivax infection enlarges the cell; Schüffner's granules may be present

Plasmodium malariae infection does not enlarge the cell

Plasmodium falciparum infection produces delicate ring forms; cells are not enlarged; Schüffner's granules are not present

Plasmodium ovale infection produces large, oval cells; Schüffner's granules are present

Clinical Conditions

- *Plasmodium* infections

Pappenheimer Body

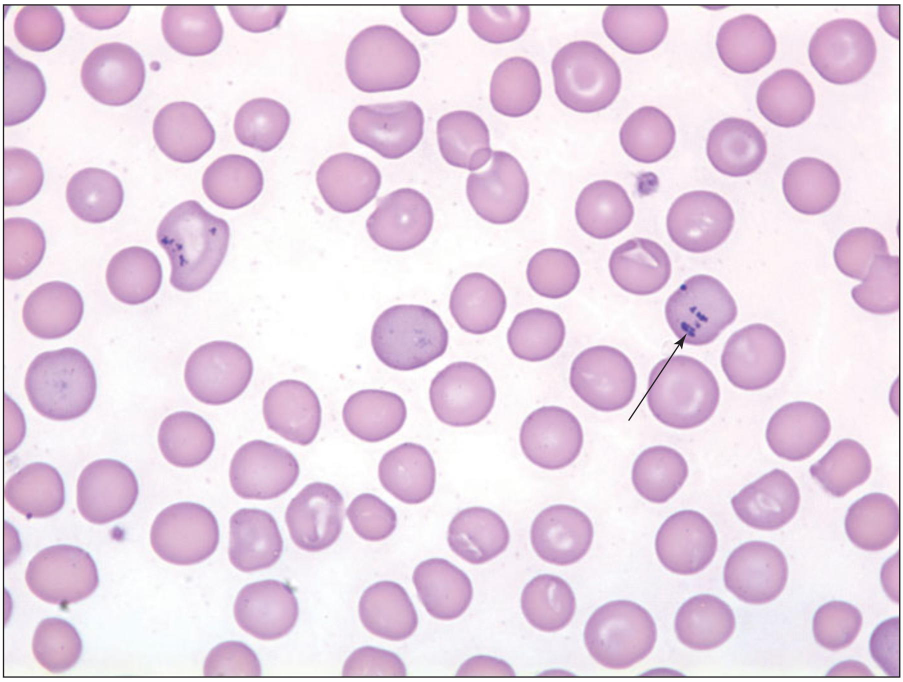


Figure IA1-50

Cell Type

Mature red blood cells, reticulocytes, metarubricytes

Description

Small, irregular, pale blue– to dark-staining granules; usually found on the periphery of the cell and in groups; smaller than Howell-Jolly bodies; represent siderosomes, which stain positive with Perls' Prussian blue stain and indicate iron content

Clinical Conditions

- Disturbed hemoglobin synthesis
- Sideroblastic anemia
- Dyserythropoietic anemias
- Thalassemia
- Myelodysplastic syndromes

ABNORMAL MATURATION

Dyserythropoiesis

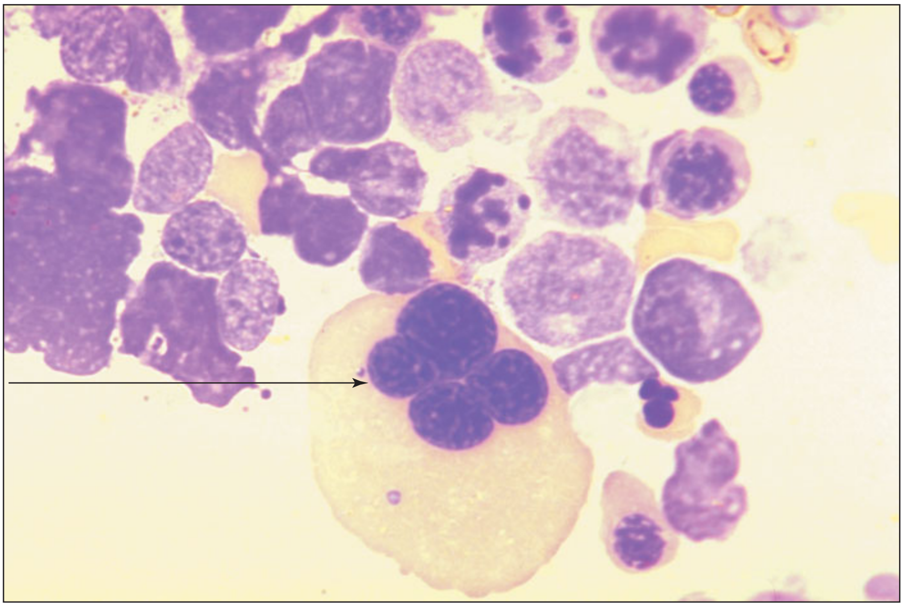


Figure IA1-51

Cell Type

Red blood cell precursors

Description

Abnormal findings in red blood cell precursors, including abnormal nuclear shapes, more than one nucleus, nuclear fragments, megaloblastoid and/or megaloblastic maturation, and vacuolated cytoplasm

Clinical Conditions

- Myelodysplastic syndromes
- Megaloblastic anemias
- Erythroleukemia (FAB–M6a)
- Pure erythroid leukemia (FAB–M6b)
- Arsenic poisoning
- Acute erythroid leukemia (WHO)

CHAPTER 2

White Blood Cells

NORMAL GRANULOCYTIC MATURATION SERIES

Neutrophilic Series

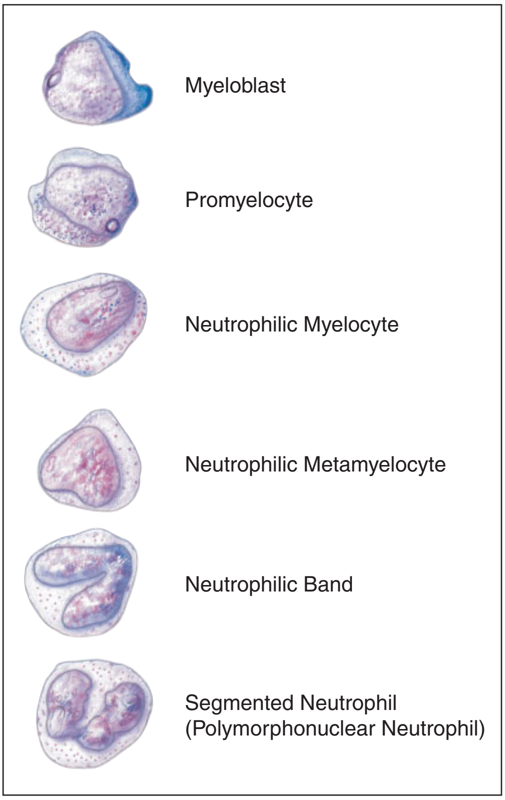

Myeloblast
Promyelocyte
Neutrophilic Myelocyte
Neutrophilic Metamyelocyte
Neutrophilic Band
Segmented Neutrophil
(Polymorphonuclear Neutrophil)

Figure IA2-1

Eosinophilic Series

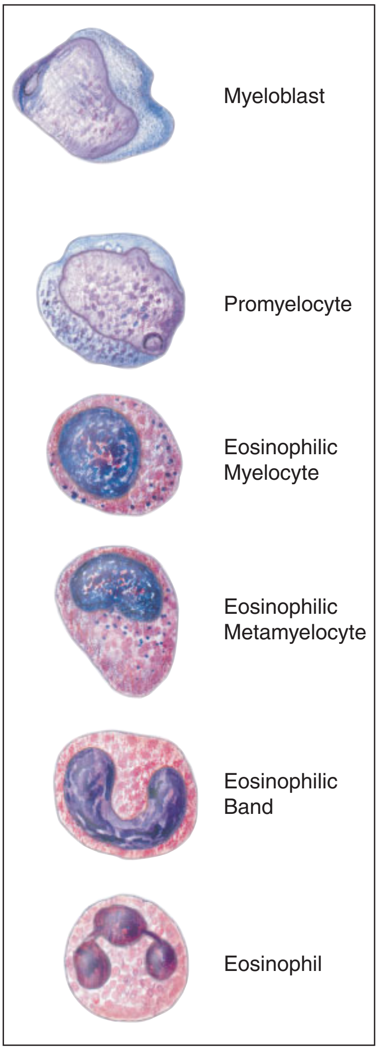

Myeloblast
Promyelocyte
Eosinophilic Myelocyte
Eosinophilic Metamyelocyte
Eosinophilic Band
Eosinophil

Figure **IA2-2**

Basophilic Series

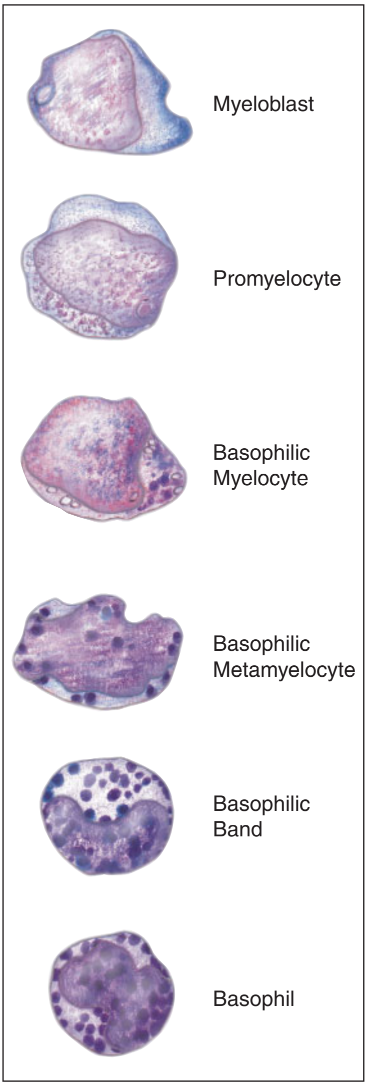

Myeloblast
Promyelocyte
Basophilic Myelocyte
Basophilic Metamyelocyte
Basophilic Band
Basophil

Figure **IA2-3**

Myeloblast

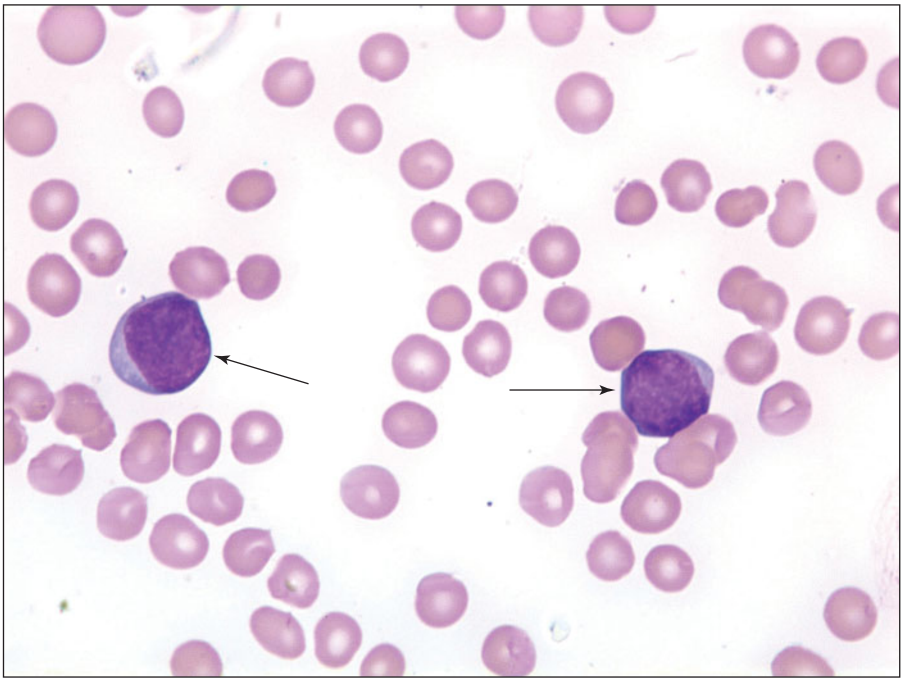


Figure IA2-4

Size: 15–20 µ

Nucleus

Shape: Round
N/C Ratio: 7:1–4:1
Color: Reddish-purple
Chromatin: Delicate and dispersed
Nucleoli: 2–3

Cytoplasm

Color: Pale to deep blue; lighter staining adjacent to nucleus
Contents: Varying amounts of granules depending on whether the blast is classified as Type I, II, or III (FAB); agranular or granular (WHO)

Clinical Conditions

- Myelodysplastic syndromes—refractory anemia with excess blasts (RAEB) 1, (RAEB) 2
- Myeloproliferative diseases—CML, PMF
- Acute myelocytic leukemia minimally differentiated (M0) (FAB)
- Acute myelocytic leukemia without maturation (M1) (FAB)
- Acute myelocytic leukemia with maturation (M2) (FAB)
- Acute promyelocytic leukemia (M3) (FAB)
- Acute myelomonocytic leukemia (M4) (FAB)
- Erythroleukemia (M6a) (FAB)
- Acute myelocytic leukemia with multilineage dysplasia
- Acute monoblastic leukemia (M5a)—<20% myeloblasts (FAB)
- Acute monocytic leukemia (M5b)—<20% myeloblasts (FAB)
- AML with t(8;21) (WHO)
- AML with t(15;17) (WHO)

Promyelocyte

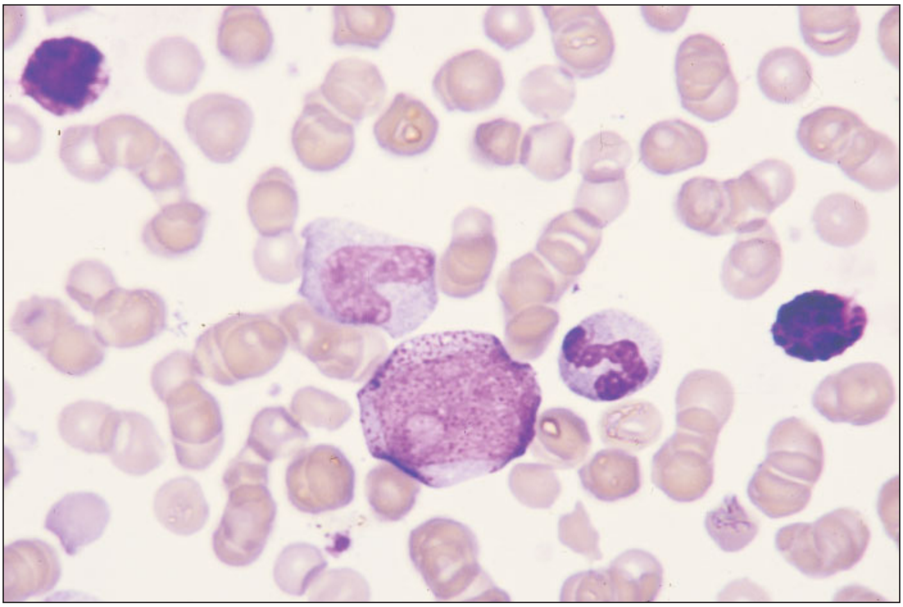


Figure IA2-5

Size: 18–25 µ

Nucleus

Shape: Round or oval; central or eccentric
N/C Ratio: 2:1–5:1
Color: Purple
Chromatin: Relatively fine, becoming coarser
Nucleoli: 2–3, varying from visible to indistinct

Cytoplasm

Color: Blue; lighter staining adjacent to nucleus
Contents: Few to many dark blue or reddish-blue primary granules

Clinical Conditions

- Acute myelocytic leukemia with maturation (M2) (FAB)
- Acute promyelocytic leukemia (M3) (FAB)
- Myeloproliferative diseases—CML, PMF
- Growth factor therapy
- Severe infections
- Acute myelomonocytic leukemia (M4) (FAB)
- Acute myelocytic leukemia with multilineage dysplasia
- AML with t(8;21) (WHO)
- AML with t(15;17) (WHO)

Neutrophilic Myelocyte

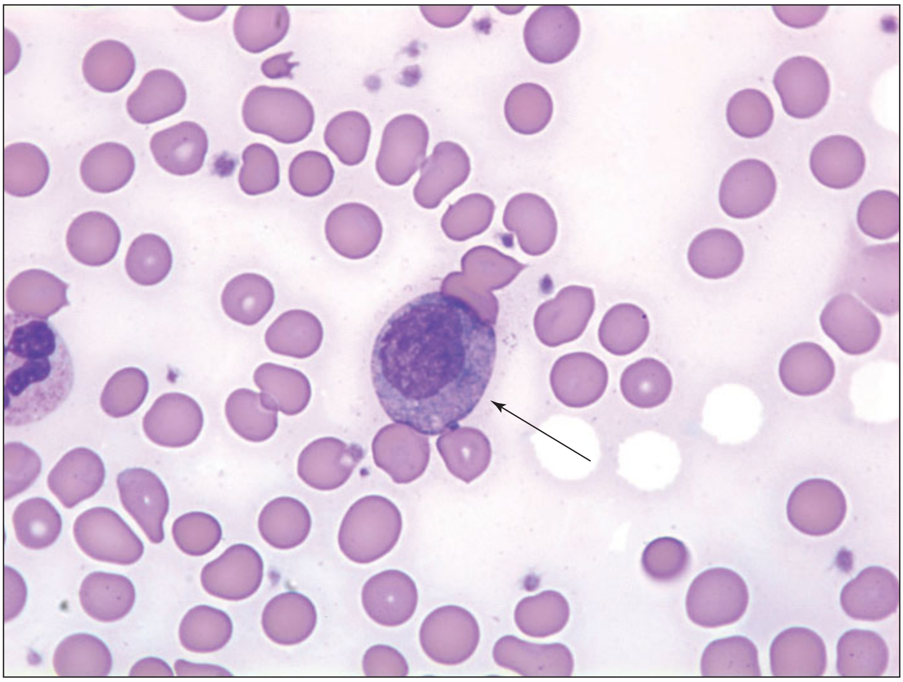


Figure IA2-6

Size: 12–18 µ

Nucleus

Shape: Round, oval, or flattened on one side
N/C Ratio: 3:1–3:2
Color: Dark purple
Chromatin: Coarser chromatin pattern
Nucleoli: Early myelocytes may have visible nucleoli

Cytoplasm

Color: Pinkish-blue
Contents: Variable numbers of nonspecific granules; small, pinkish to reddish specific granules first appearing next to the nucleus and then throughout the cytoplasm

Clinical Conditions

- Acute myelocytic leukemia with maturation (M2) (FAB)
- Growth factor therapy
- Myeloproliferative diseases—CML, PMF
- Stress
- Severe infections
- AML with t(8;21) (WHO)

Eosinophilic Myelocyte

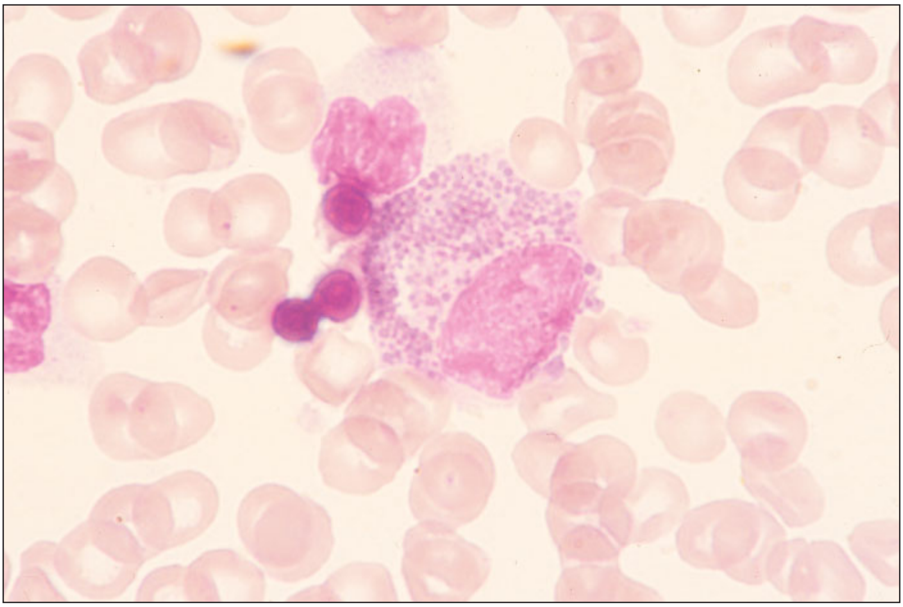


Figure IA2-7

Size: 12–18 µ

Nucleus

Shape: Round, oval, or flattened on one side
N/C Ratio: 3:1–3:2
Color: Dark purple
Chromatin: Courser chromatin pattern
Nucleoli: Early myelocytes may have visible nucleoli

Cytoplasm

Color: Pinkish-blue
Contents: Numerous large, round specific granules staining orange-brown to orange-blue; variable numbers of nonspecific granules

Clinical Conditions

- Chronic eosinophilic leukemia (NOS) (WHO)
- Hypereosinophilic syndrome
- PDGFRA rearrangement (WHO)
- PDGFRB rearrangement (WHO)
- FGFR1 rearrangement (WHO)

BASOPHILIC MYELOCYTE

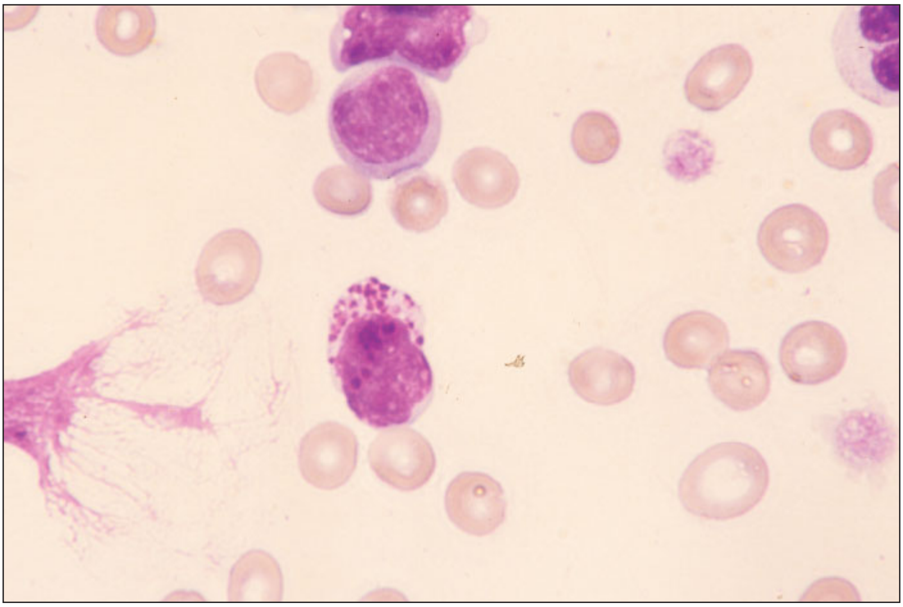


Figure IA2-8

Size: 12–18 μ

Nucleus

Shape: Round, oval, or flattened on one side
N/C Ratio: 3:1–3:2
Color: Dark purple
Chromatin: Coarser chromatin pattern
Nucleoli: Early myelocytes may have visible nucleoli

Cytoplasm

Color: Pinkish-blue
Contents: Few large specific granules staining dark bluish–purple to bluish-black

Clinical Conditions

- Acute basophilic leukemia
- CML
- AML with t(6;9) (WHO)

Neutrophilic Metamyelocyte

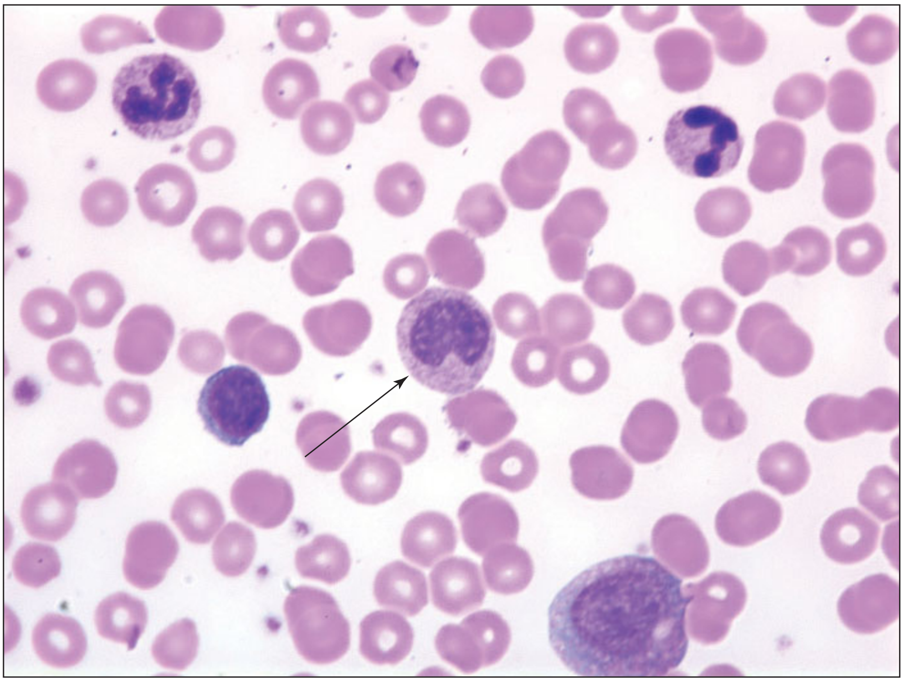


Figure IA2-9

Size: 10–15 μ

Nucleus

Shape: Typical kidney shape or slightly indented
N/C Ratio: 7:3–1:1
Color: Dark purple
Chromatin: Coarse, purple chromatin
Nucleoli: None

Cytoplasm

Color: Pink-blue
Contents: Pinkish to reddish-blue granules

Clinical Conditions

- Growth factor therapy
- Stress
- Severe infections
- Myeloproliferative diseases—CML, PMF
- AML with maturation (M_2) (FAB)
- AML with t(8;21) (WHO)

Eosinophilic Metamyelocyte

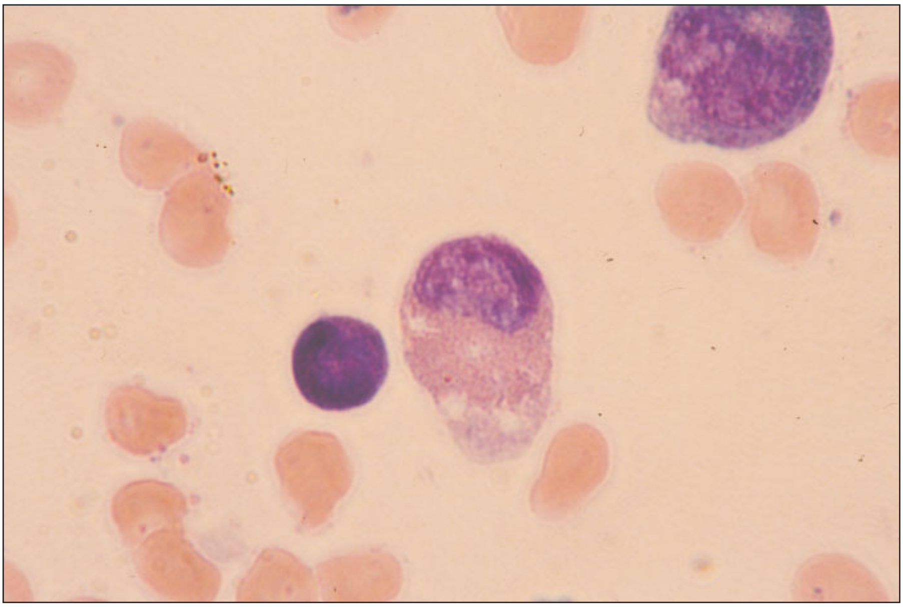


Figure IA2-10

Size: 10–15 µ

Nucleus

Shape: Typical kidney shape or slightly indented
N/C Ratio: 7:3–1:1
Color: Dark purple
Chromatin: Coarse blue-black
Nucleoli: None

Cytoplasm

Color: Pink-blue
Contents: Numerous medium bright orange to reddish granules

Clinical Conditions

- Parsitic infections
- Chronic eosinophilic leukemia (NOS) (WHO)
- PDGFRA rearrangement (WHO)
- PDGFRB rearrangement (WHO)
- FGFR1 rearrangement (WHO)

Basophilic Metamyelocyte

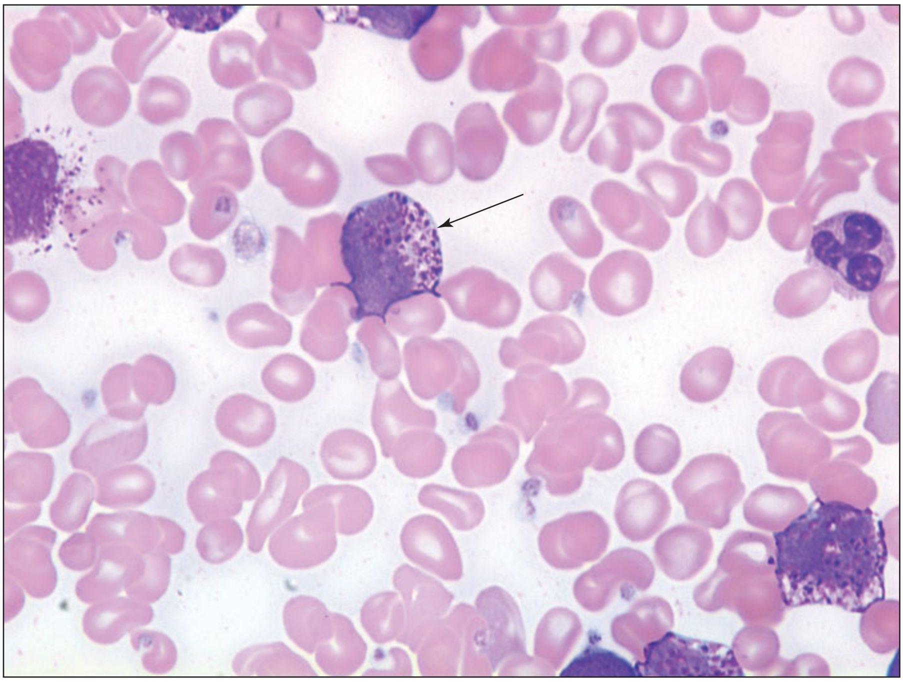


Figure IA2-11

Size: 10–15 µ

Nucleus

Shape: Typical kidney shape or slightly indented
N/C Ratio: 7:3–1:1
Color: Dark purple
Chromatin: Coarse, blue-black
Nucleoli: None

Cytoplasm

Color: Pink-blue
Contents: Few large dark blue–black granules

Clinical Conditions

- CML
- Basophilic leukemia (WHO)
- AML with t(6;9) (WHO)

Neutrophilic Band

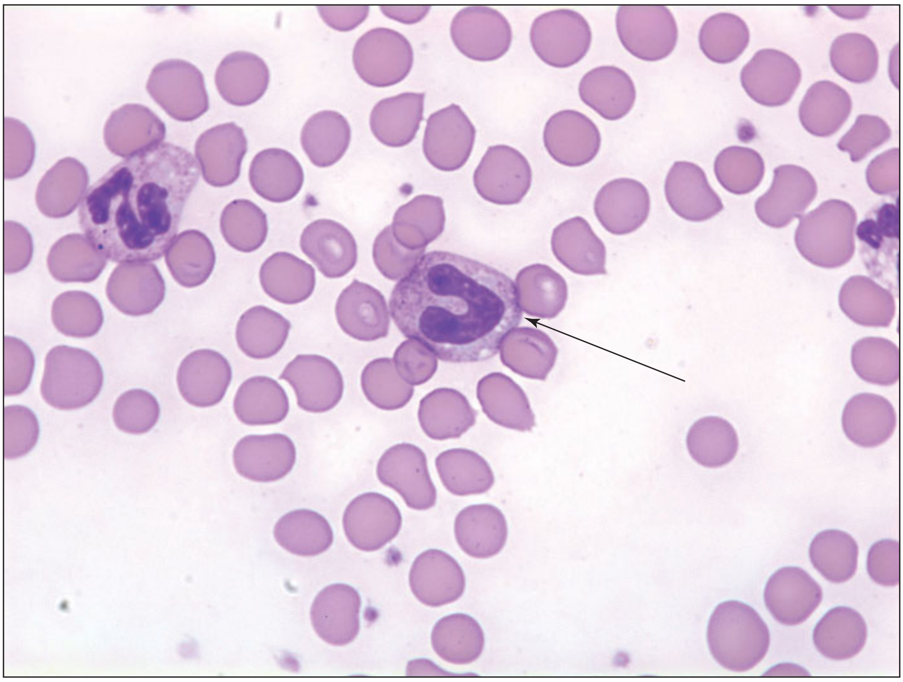


Figure IA2-12

Size: 10–16 μ

Nucleus

Shape: Band shaped or markedly indented; indentation is greater than one-half the width of the hypothetical round nucleus

N/C Ratio: 1:1–1:2

Color: Dark purple

Chromatin: Coarse, blue-black

Cytoplasm

Color: Pink-blue

Contents: Pinkish-blue granules

Clinical Conditions

- Growth factor therapy
- Stress
- Infections
- Myeloproliferative diseases—CML, PMF
- AML with maturation (M_2) (FAB)
- AML with t(8;21) (WHO)

Eosinophilic Band

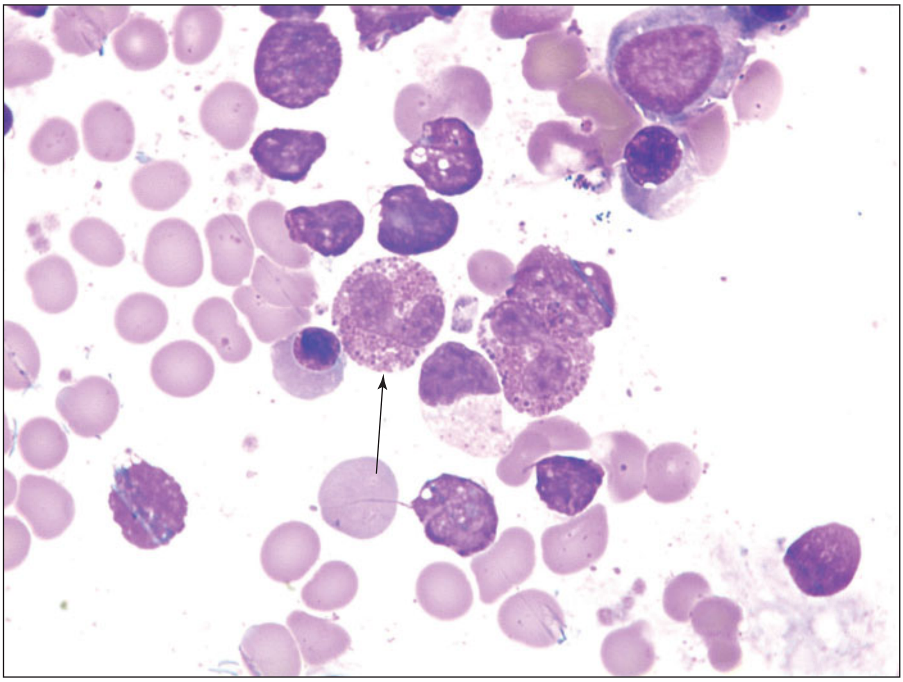


Figure IA2-13

Size: 10–16 µ

Nucleus

Shape: Band shaped or markedly indented
N/C Ratio: 1:1–1:2
Color: Dark purple
Chromatin: Coarse, blue-black
Nucleoli: None

Cytoplasm

Color: Pink-blue
Contents: Numerous orange-red granules

Clinical Conditions

- Parasitic infections
- Chronic eosinophilic leukemia (NOS) (WHO)
- PDGFRA rearrangement (WHO)
- PDGFRB rearrangement (WHO)
- FGFR1 rearrangement (WHO)

Basophilic Band

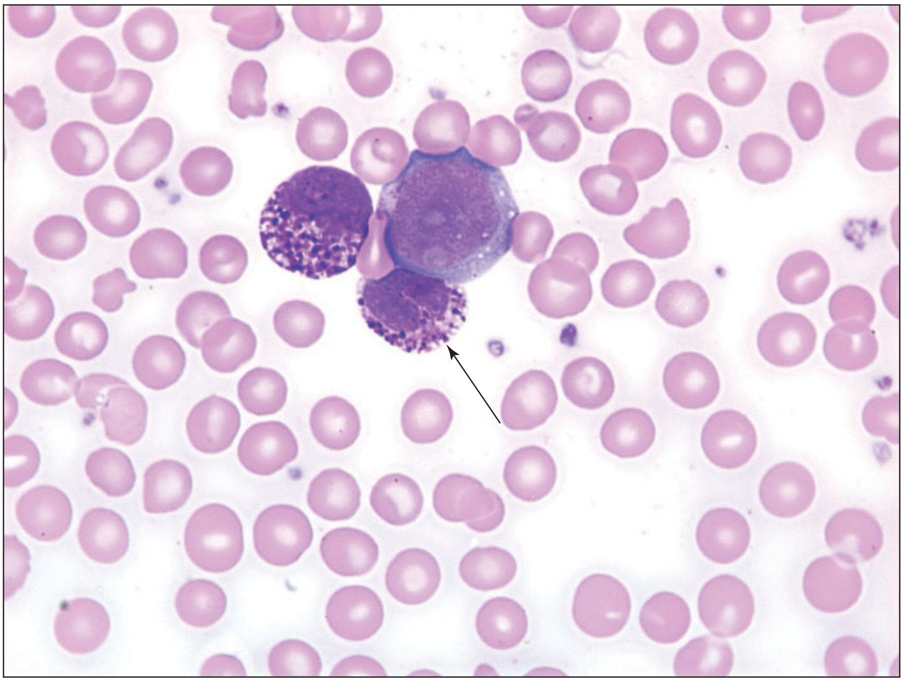


Figure IA2-14

Size: 10–16 μ

Nucleus

Shape: Band shaped or markedly indented
N/C Ratio: 1:1–1:2
Color: Dark purple
Chromatin: Coarse, blue-black
Nucleoli: None

Cytoplasm

Color: Pink-blue
Contents: Few large dark bluish–purple to bluish-black granules

Clinical Conditions

- Myeloproliferative diseases—CML, PMF
- Basophilic leukemia (WHO)
- AML with t(6;9) (WHO)

Segmented Neutrophil (Polymorphonuclear Neutrophil)

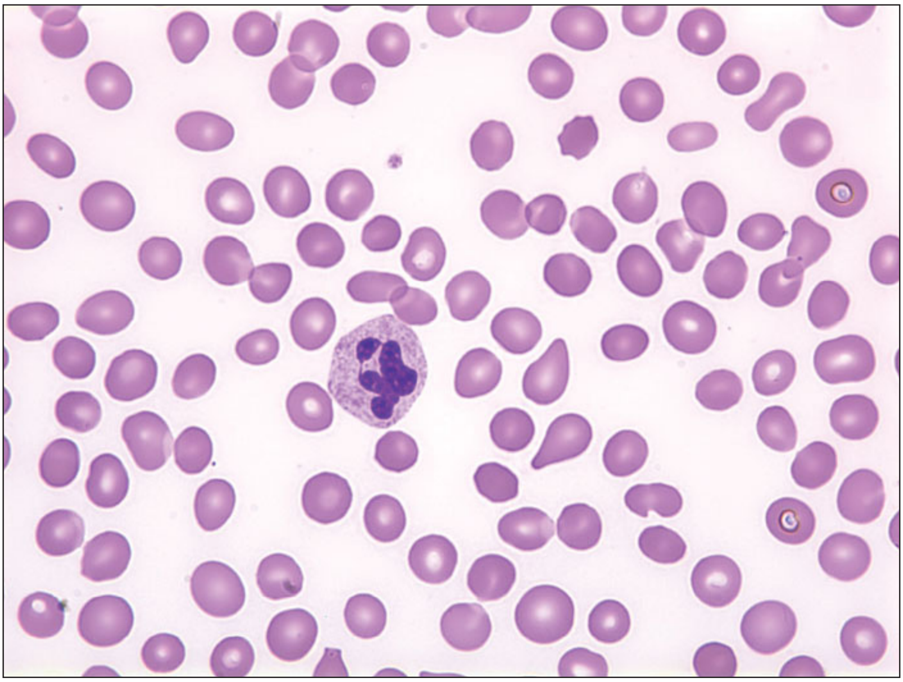


Figure IA2-15

Size: 10–16 µ

Nucleus

Shape: 2–5 lobes connected by a very narrow filament; nuclear indentation is greater than one-half its diameter
N/C Ratio: 1:3–1:5
Color: Dark purple
Chromatin: Heavily clumped
Nucleoli: None

Cytoplasm

Color: Light pink to bluish
Contents: Many small, evenly distributed pink to rose-violet granules

Clinical Conditions

- Infections
- Chronic neutrophilic leukemia
- Growth factor therapy
- Stress

Eosinophil

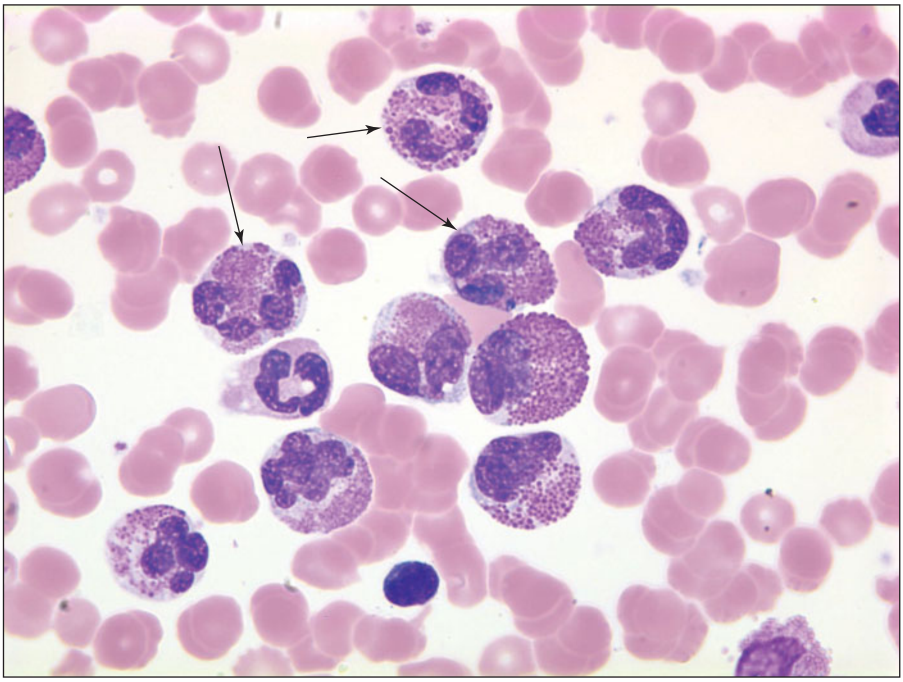


Figure IA2-16

Size: 10–16 μ

Nucleus

Shape: 2–3 lobes
N/C Ratio: 1:3–1:5
Color: Dark purple
Chromatin: Heavily clumped
Nucleoli: None

Cytoplasm

Color: Pink-blue
Contents: Many large, round, uniform reddish-orange granules

Clinical Conditions

- Protozoan infections
- Allergic disorders
- Chronic myelocytic leukemia
- Dermatitis
- Hodgkin lymphoma
- Chronic eosinophilic leukemia (NOS) (WHO)
- PDGFRA rearrangement (WHO)
- PDGFRB rearrangement (WHO)
- FGFR1 rearrangement (WHO)

Basophil

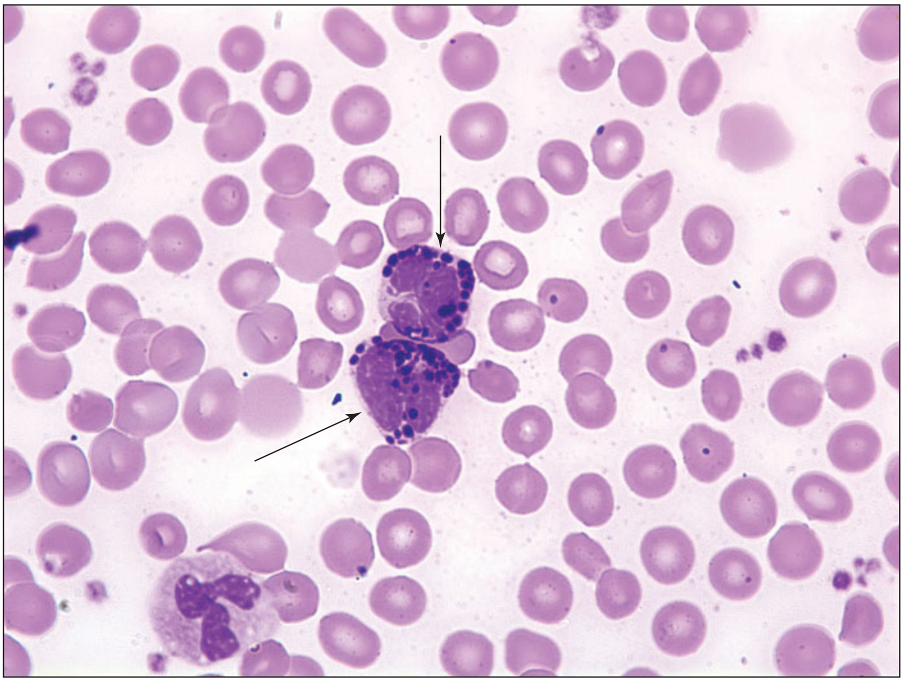


Figure IA2-17

Size: 10–16 µ

Nucleus

Shape: 2 lobes usually obscured by granules
N/C Ratio: 1:3–1:5
Color: Dark purple
Chromatin: Heavily clumped
Nucleoli: None

Cytoplasm

Color: Pink-blue
Contents: Few dark blue–black granules

Clinical Conditions

- Acute basophilic leukemia
- Myeloproliferative diseases
- Allergy and inflammation
- AML with t(6;9) (WHO)

Mast Cell

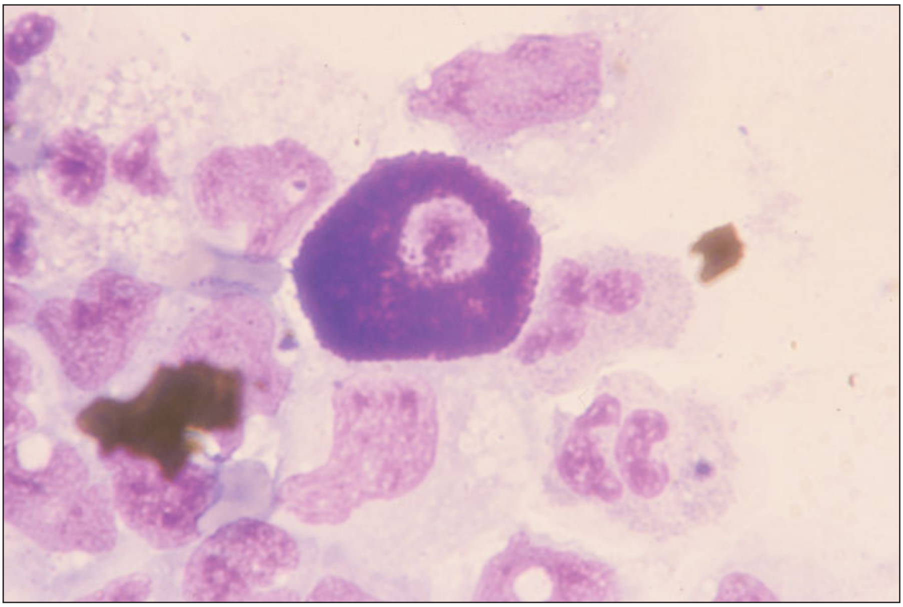


Figure IA2-18

Size: 9–12 μ

Nucleus

Shape: Round
N/C Ratio: 1:1
Color: Dark purple
Chromatin: Heavily clumped
Nucleoli: None

Cytoplasm

Color: Dark blue
Contents: Many dark blue granules

Clinical Condition

- Mast cell disease

NUCLEAR SEGMENTATION

Hypersegmentation

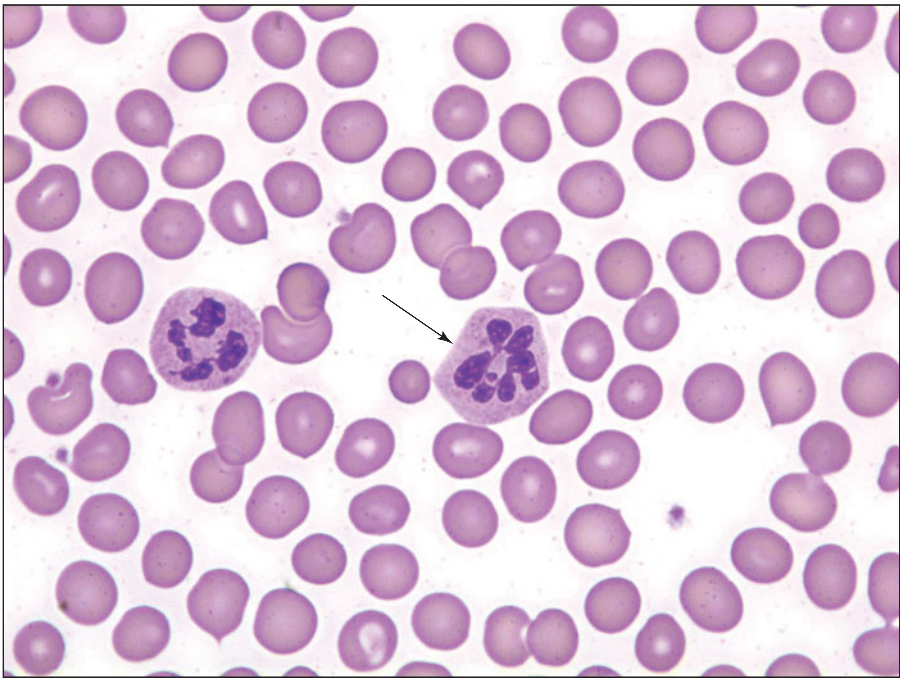


Figure IA2-19

Cell Type

Neutrophil, eosinophil

Description

Neutrophil has six or more nuclear lobes; eosinophil has greater than four lobes

Clinical Conditions

- Chronic infections
- B_{12} deficiency
- Folic acid deficiency
- Myelodysplastic syndromes
- Hereditary hypersegmentation
- Long-term infections

Pelger-Huët

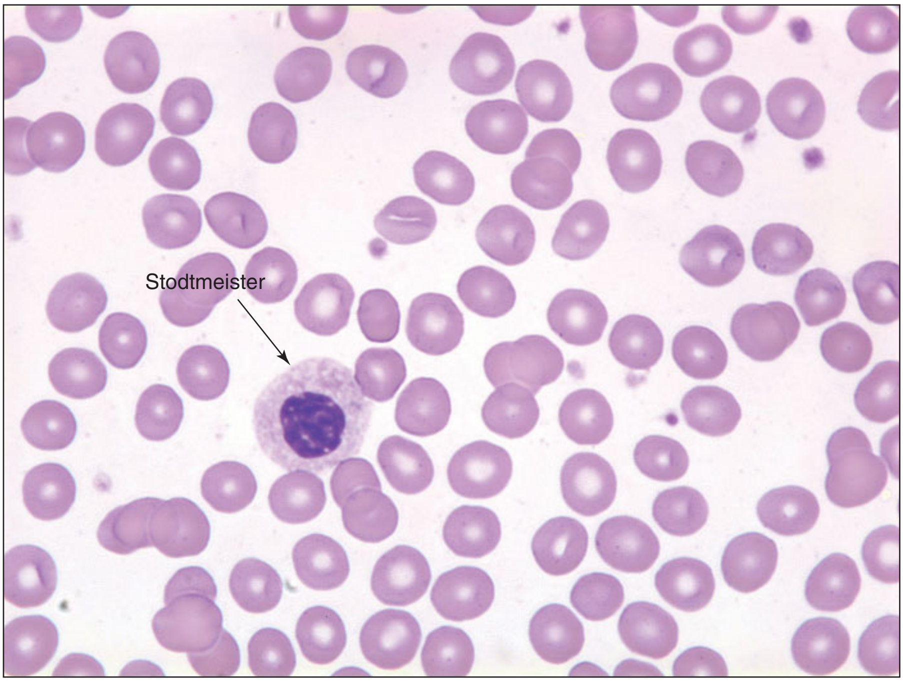

Stodtmeister

Figure **IA2-20a**

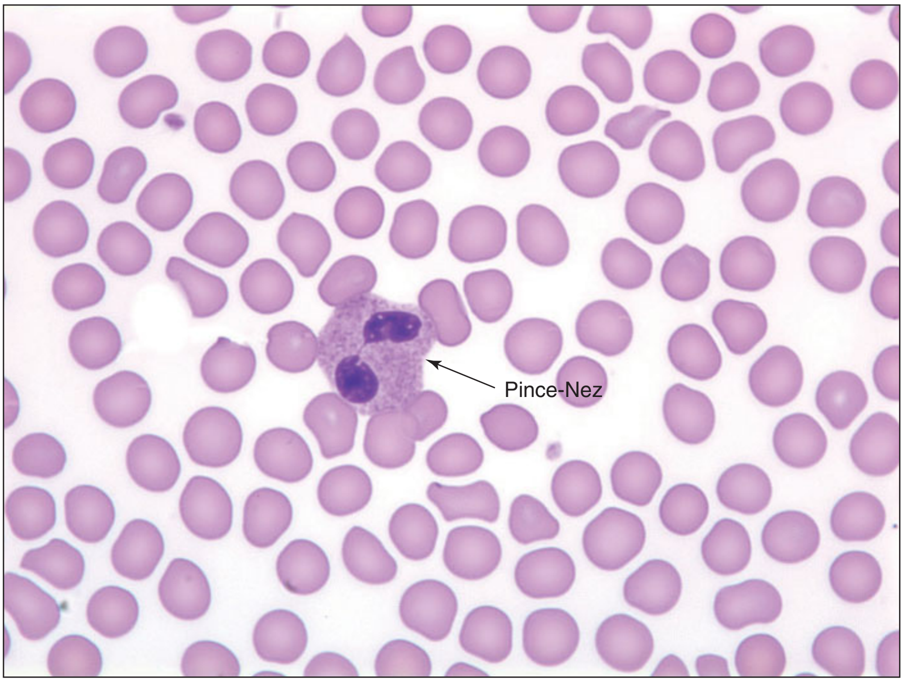


Figure **IA2-20b**

Cell Type

Neutrophil

Description

Heterozygous inherited disorder (Pince-Nez)

Bilobed or dumbbell-shaped nucleus; clumped, coarse chromatin; normal cytoplasmic granules

Homozygous inherited disorder (Stodtmeister)

Round or oval nuclei; dense clumped coarse chromatin; normal cytoplasmic granules

Clinical Condition

- Pelger-Huët—inherited disorder (autosomal dominant)

Pelgeroid Cells

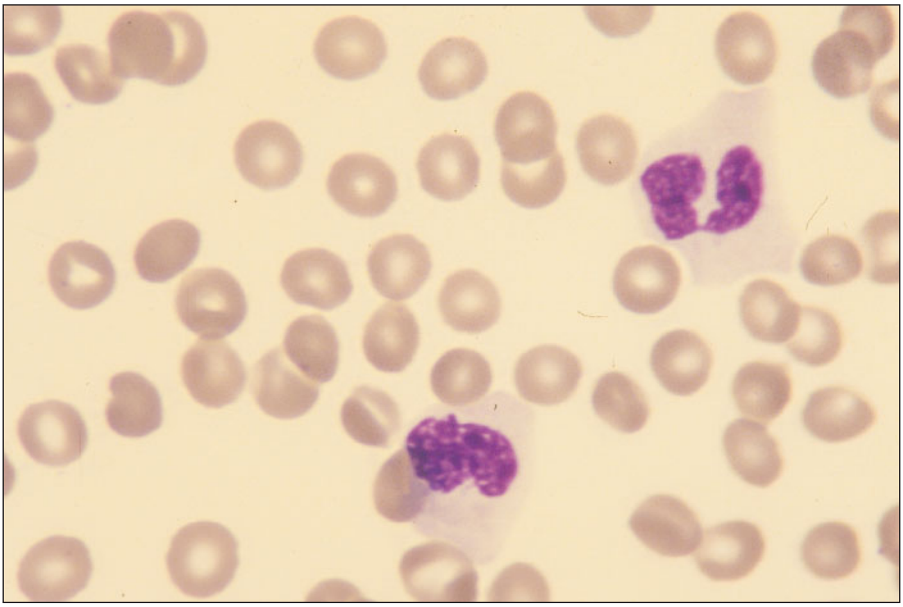


Figure **IA2-21**

Cell Type

Neutrophil

Description

Nucleus resembles Pelger-Huët (round or bilobed); few or no cytoplasmic granules

Clinical Conditions

- Myelodysplastic syndromes
- Acute myelogenous leukemias—dysplastic finding
- Myelodysplastic/myeloproliferative diseases

CYTOPLASMIC INCLUSIONS

Alder-Reilly Bodies

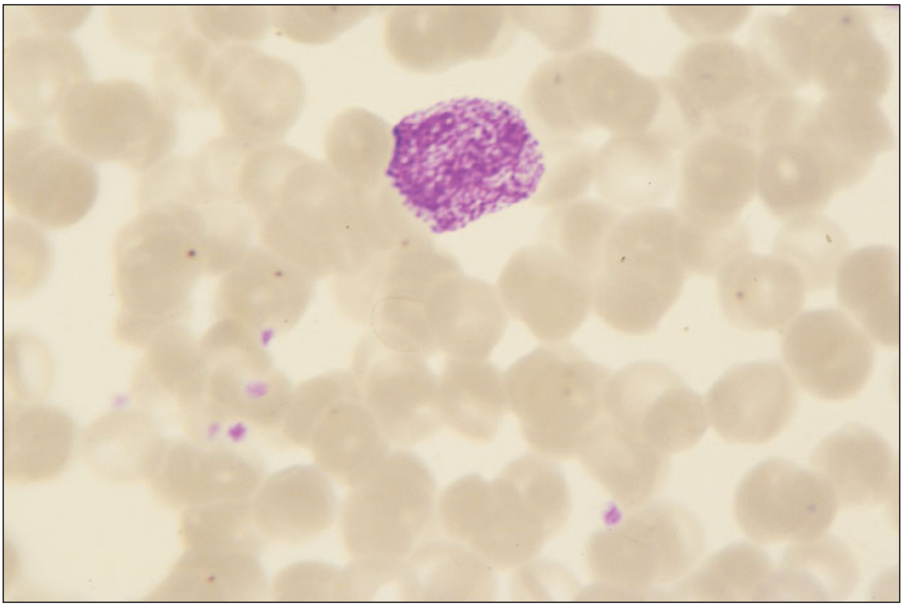


Figure **IA2-22**

Cell Type

Neutrophil, eosinophil, basophil; occasionally lymphocyte and monocyte

Description

Inherited condition (autosomal recessive)

Dense blue cytoplasmic granules consisting of stored mucopolysaccharides and sphingomyelin

Normal nuclear maturation

Clinical Condition

- Mucopolysaccharidoses (e.g., Hurler's syndrome, Hunter's syndrome)

Auer Rods

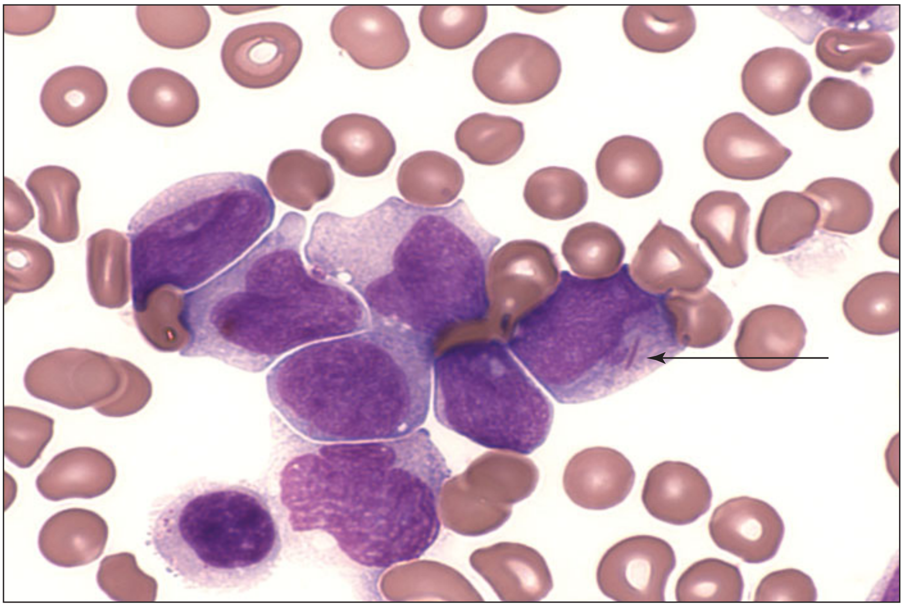


Figure **IA2-23**

Cell Type

Myeloblast and monoblast (rare)

Description

Reddish-purple, rod-shaped cytoplasmic inclusions
Alignment of primary granules

Clinical Conditions

- Acute myelocytic leukemia without maturation (M1) (FAB)
- Acute myelocytic leukemia with maturation (M2) (FAB)
- Acute promyelocytic leukemia (M3) (FAB)
- Acute myelomonocytic leukemia (M4) (FAB)
- Erythroleukemia (M6a) (FAB)
- Acute myelocytic leukemia with multilineage dysplasia
- Chronic myelocytic leukemia in blastic transformation
- AML with t(8;21) (WHO)
- AML with t(15;17) (WHO)
- AML with inv 16 or t(16;16) (WHO)

Chédiak-Higashi Granules

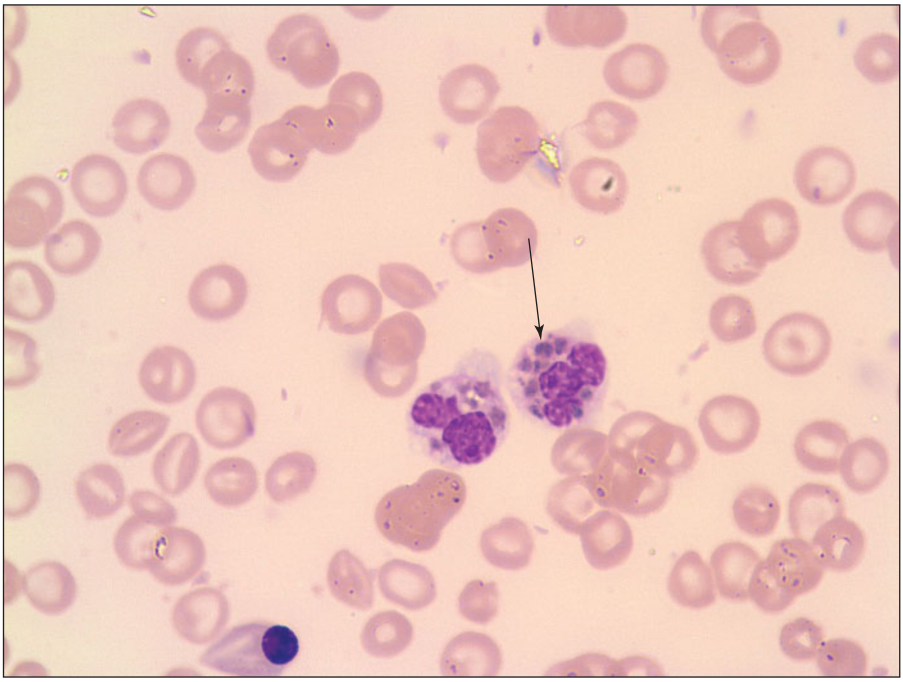


Figure **IA2-24**

Cell Type

Granulocyte, lymphocyte, monocyte

Description

Inherited (autosomal recessive)

Many large, greenish primary cytoplasmic granules or many large, reddish-purple secondary cytoplasmic granules

Clinical Condition

- Chédiak-Higashi Syndrome—severe and often fatal infections in children; complete or partial albinism

Döhle Body

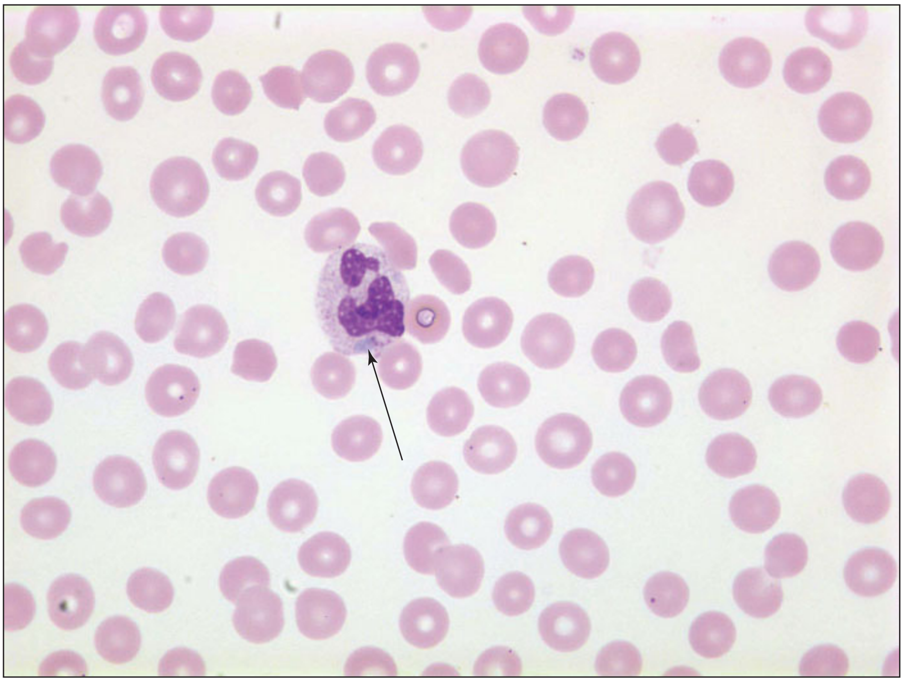


Figure **IA2-25**

Cell Type

Neutrophil

Description

Round or rod-shaped, light-blue cytoplasmic inclusions, often located near cell membrane

Inclusions represent ribosomes or rough endoplasmic reticulum

Clinical Conditions

- Infections
- Drug intoxication
- Burns
- Myelodysplastic syndromes, often seen in the degranulated segmented cells
- May-Hegglin anomaly
- Pregnancy
- Growth factor therapy

Faggot Cell

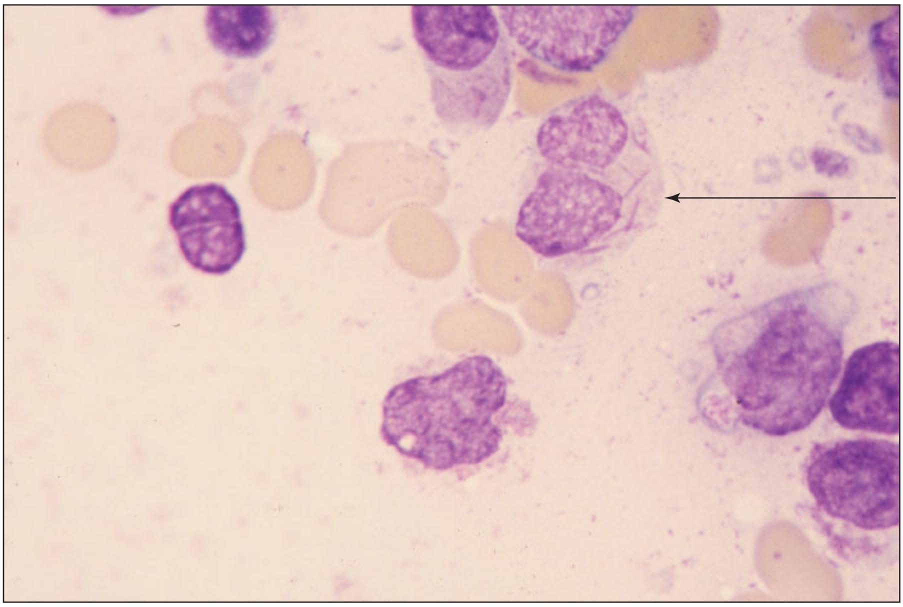


Figure IA2-26

Cell Type

Promyelocyte

Description

Groups or stacks of cigar-shaped rods in cytoplasm

Clinical Conditions

- Acute promyelocytic leukemia (M3, M3v) (FAB)
- AML with t(15;17) (WHO)

May-Hegglin Inclusion

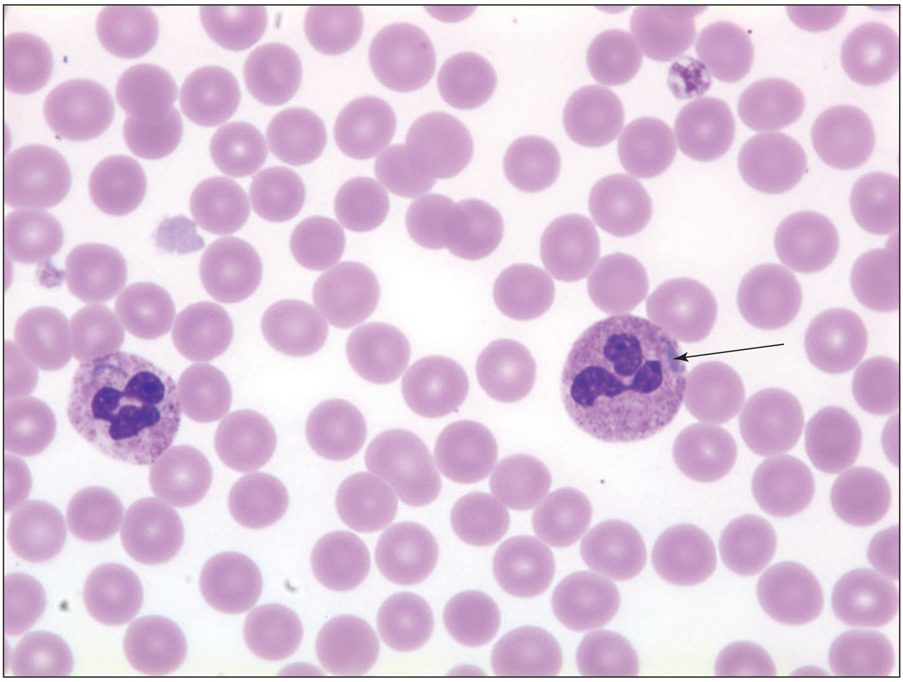


Figure IA2-27

Cell Type

Neutrophil, eosinophil, basophil, monocyte

Description

Inherited (autosomal dominant)
Large, blue, crescent-shaped cytoplasmic inclusions consisting of RNA
Resemble large Döhle bodies
Presence of enlarged platelets

Clinical Condition

- May-Hegglin anomaly

Microorganisms

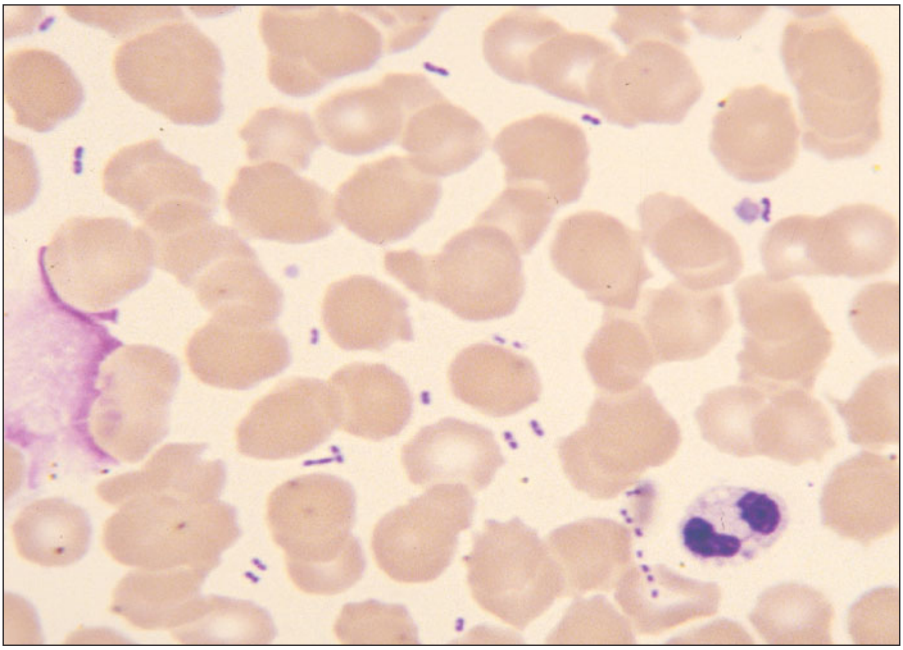


Figure **IA2-28**

Cell Type

Neutrophil, monocyte

Description

Microorganisms in cytoplasm

Clinical Condition

- Microbial infections

Toxic Granulation

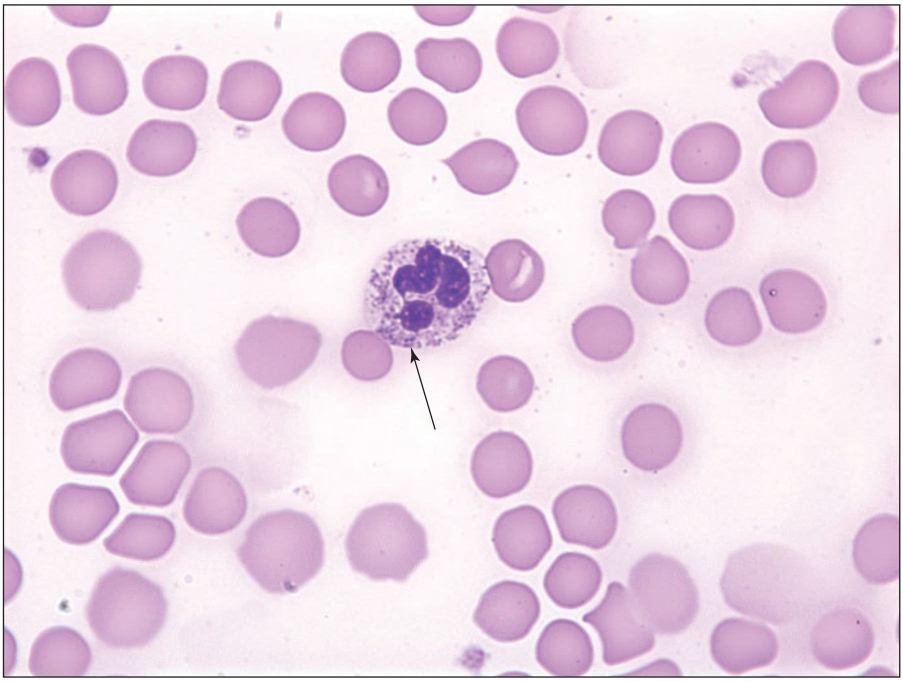


Figure **IA2-29**

Cell Type

Neutrophil

Description

Heavy, coarse, dark-blue primary cytoplasmic granules
Strong peroxidase reactivity

Clinical Conditions

- Infections
- Burns
- Drug intoxication
- Inflammation
- Growth factor therapy

Vacuolization

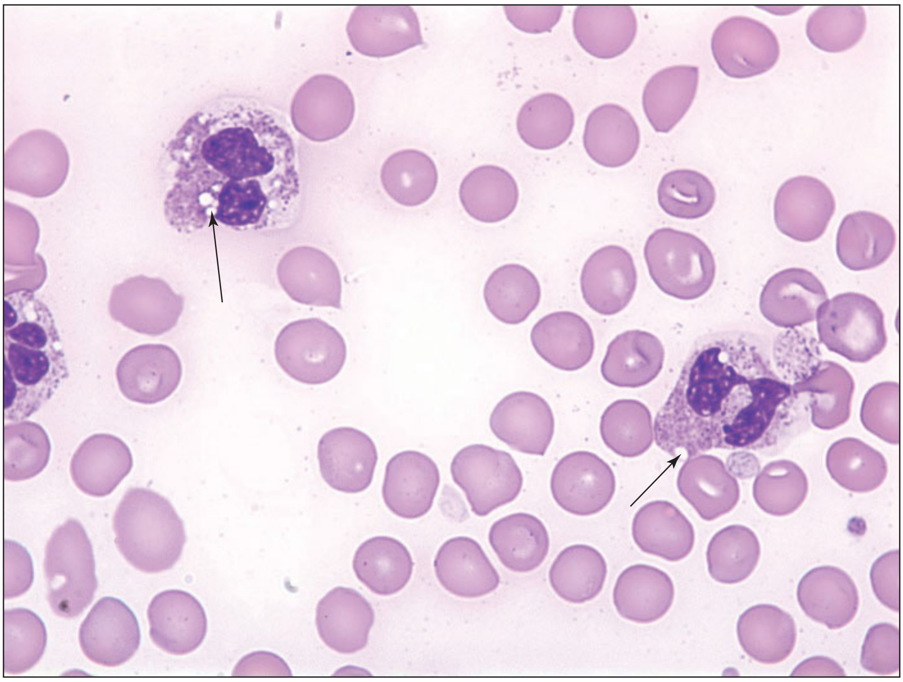


Figure IA2-30

Cell Type

Neutrophil, monocyte

Description

Vacuoles (holes) in cytoplasm

Clinical Conditions

- Severe infection
- Cell degeneration
- Phagocytosis
- Burns
- Toxins

LE Cell

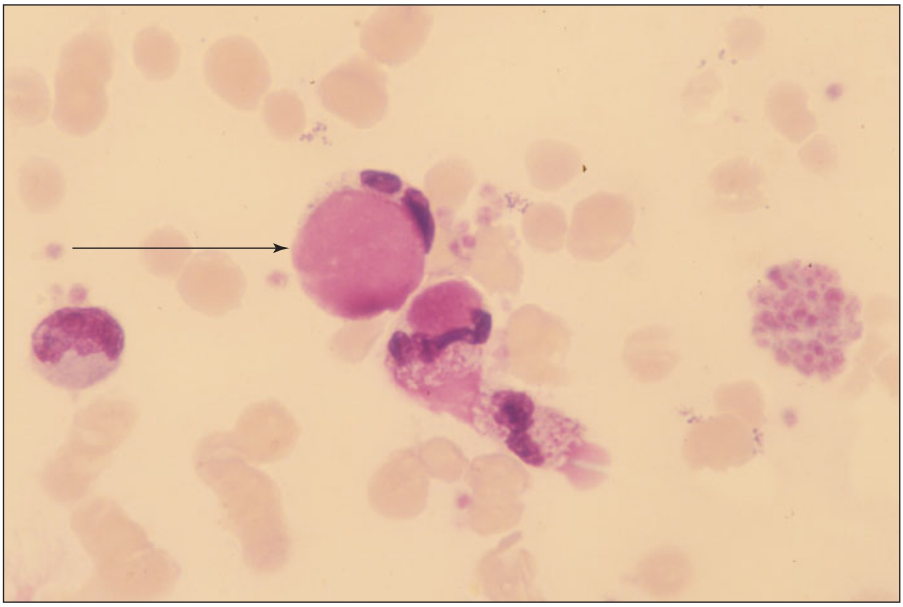


Figure **IA2-31**

Cell Type

Neutrophil

Description

Large, spherical body in cytoplasm is homogeneous, has no nuclear structure, and stains pale purple; nucleus of cell is pushed to periphery and appears to wrap around cytoplasmic inclusion

Clinical Condition

- Systemic lupus erythematosus

MALIGNANT GRANULOCYTES

Type I Myeloblast (FAB); Agranular Blast (WHO)

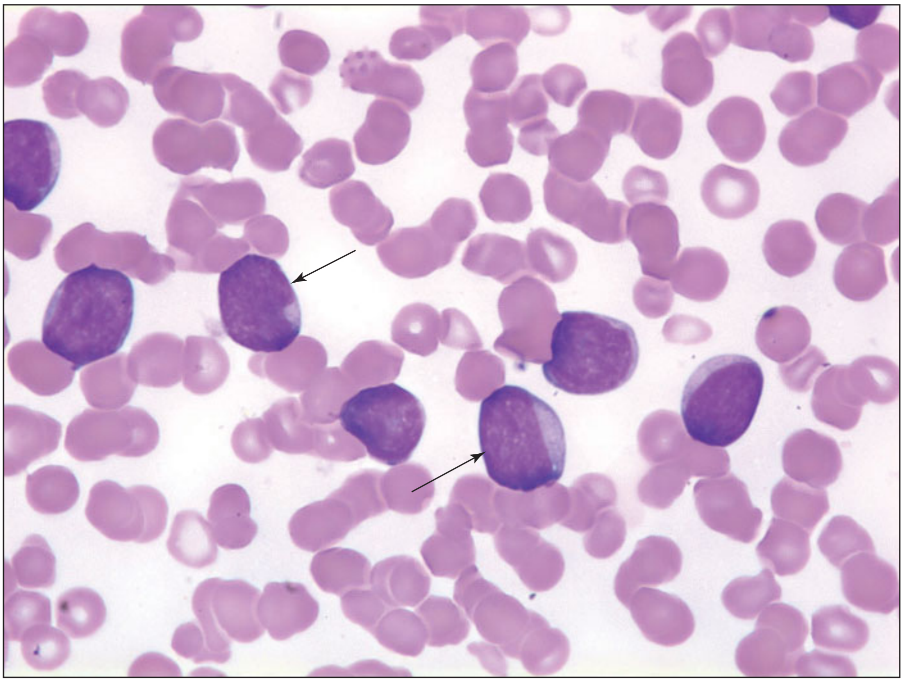


Figure IA2-32

Size: 14–18 μ

Nucleus

Shape: Oval or round
N/C Ratio: 6:1–7:1
Color: Dark purple
Chromatin: Fine
Nucleoli: 1–3

Cytoplasm

Color: Light to medium blue
Contents: Without azurophilic granules

Clinical Conditions

- Acute myelocytic leukemia minimally differentiated (M0) (FAB)
- Acute myelocytic leukemia without maturation (M1) (FAB)
- Acute myelocytic leukemia with maturation (M2) (FAB)
- Acute myelomonocytic leukemia (M4) (FAB)
- Erythroleukemia (M6a) (FAB)
- Myeloproliferative diseases—CML, PMF

Type II Myeloblast (FAB); Granular Blast (WHO)

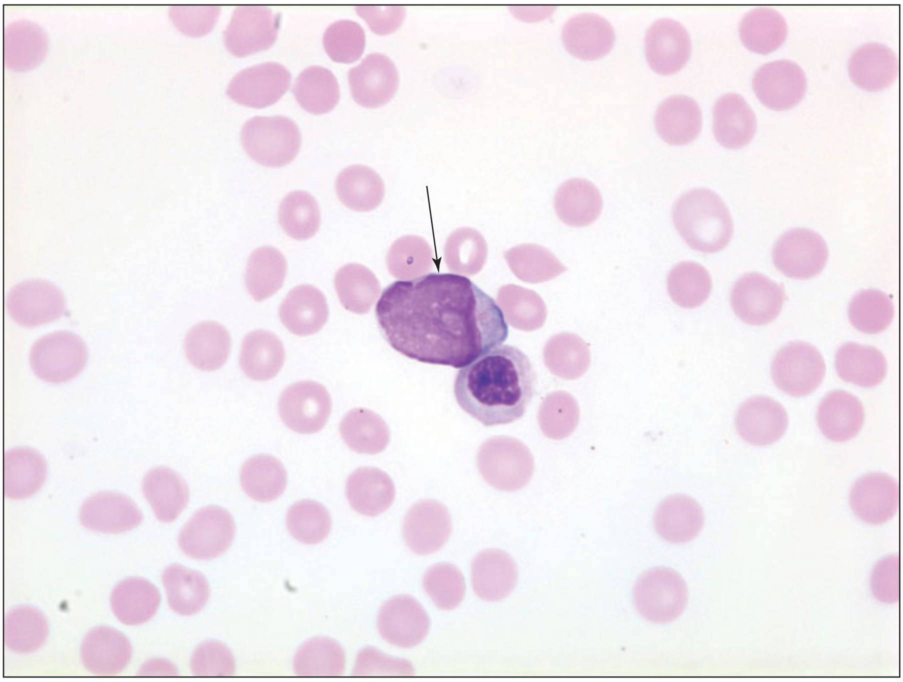


Figure IA2-33

Size: 10–18 μ

Nucleus

Shape: Oval or round
N/C Ratio: Slightly lower than a type I
Color: Dark purple
Chromatin: Slightly more condensed than a type I
Nucleoli: 2–5

Cytoplasm

Color: Medium blue
Contents: <20 azurophilic granules and may have Auer rods

Clinical Conditions

- Acute myelocytic leukemia without maturation (M1) (FAB)
- Acute myelocytic leukemia with maturation (M2) (FAB)
- Acute myelomonocytic leukemia (M4) (FAB)
- Erythroleukemia (M6a) (FAB)
- Myeloproliferative diseases—CML, PMF
- AML with t(8;21) (WHO)

Type III Myeloblast (FAB); Granular Blast (WHO)

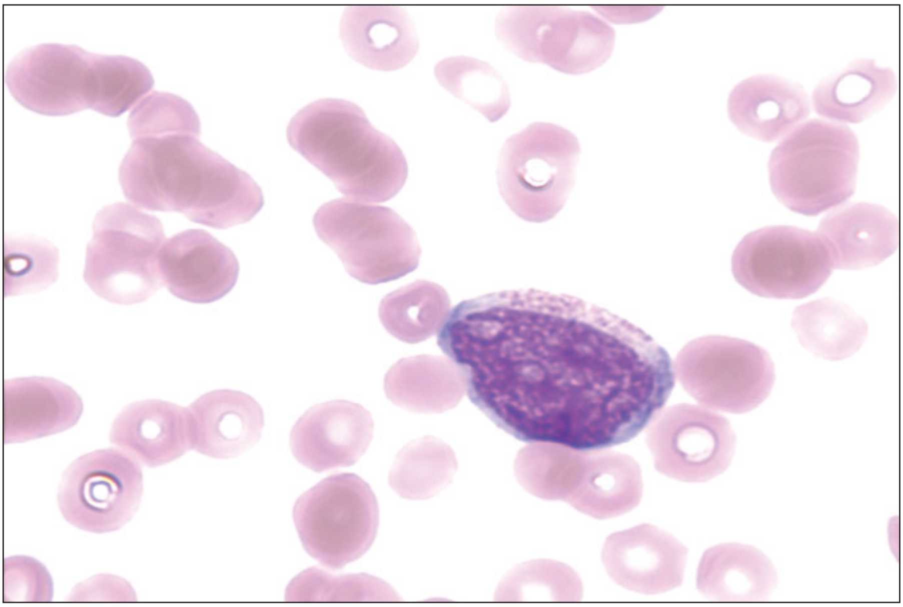


Figure IA2-34

Size: 10–18 μ

Nucleus

Shape: Oval or round
N/C Ratio: Lower than a type I
Location: Centrally located
Color: Dark purple
Chromatin: Slightly more condensed than type II
Nucleoli: Less visible

Cytoplasm

Color: Medium blue
Contents: >20 azurophilic granules but do not obscure the nucleus

Clinical Conditions

- Acute myelocytic leukemia with maturation (M2) (FAB)
- AML with t(8;21) (WHO)

Abnormal Promyelocyte

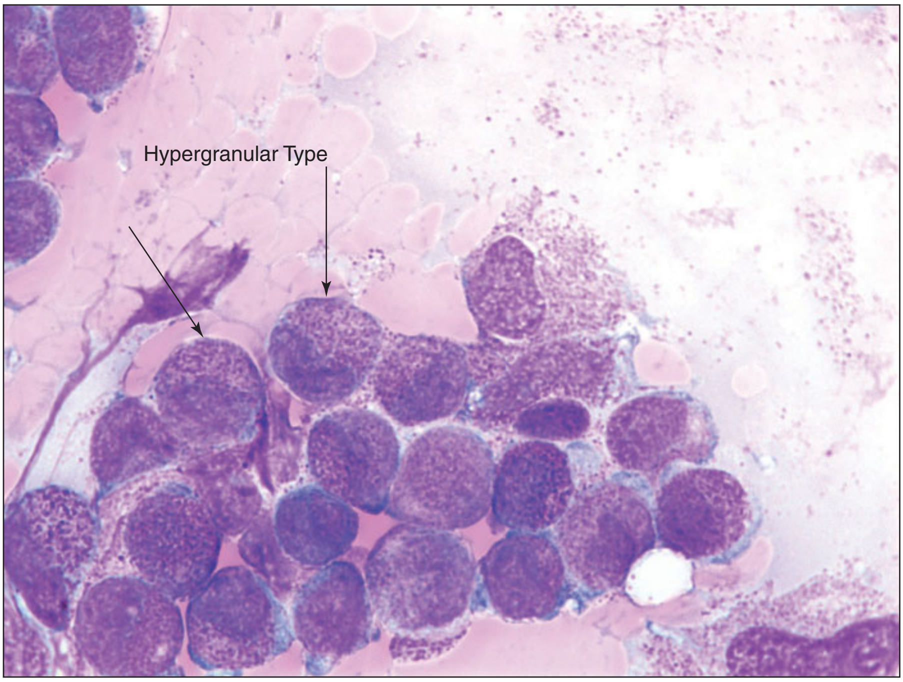

Hypergranular Type

Figure **IA2-35a**

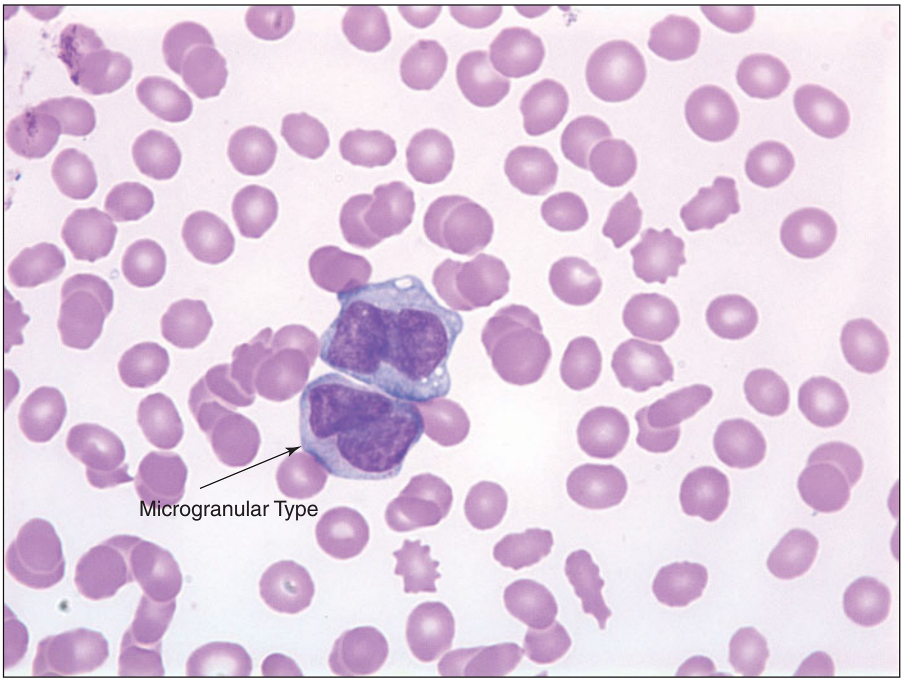

Microgranular Type

Figure **IA2-35b**

Size: 18–25 µ

Nucleus

Shape: Round or, more commonly, reniform or bilobed
N/C Ratio: 2:1
Color: Purple
Chromatin: Relatively fine, becoming coarser
Nucleoli: 2–3, varying from visible to indistinct

Cytoplasm

Hypergranular Type:
- Color: Intensely basophilic
- Contents: Large red to purple granules; Auer rods may be numerous and intertwined, giving a haystack appearance (faggot cells); may obscure the nucleus

Microgranular Type:
- Color: Moderately basophilic
- Contents: Small, indistinct granules that are difficult to see with the light microscope; Auer rods are often found but not as abundant as those found in the hypergranular type

Clinical Conditions

- Acute promyelocytic leukemia (M3, M3v) (FAB)
- AML with t(15;17) (WHO)

ABNORMAL MATURATION

Dysgranulopoiesis

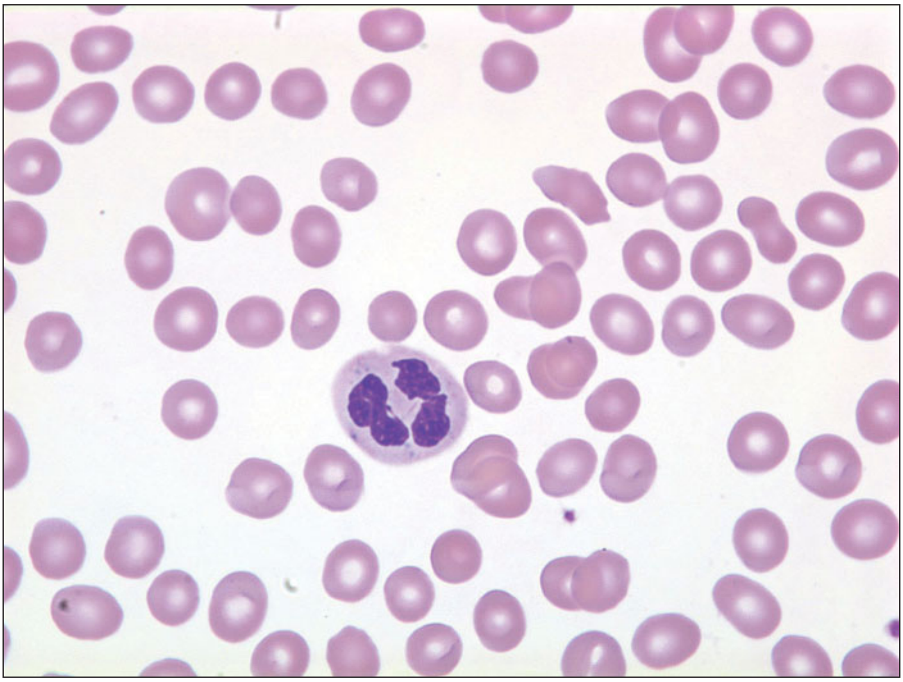


Figure **IA2-36**

Cell Type

Granulocyte cell line

Description

Nuclear/cytoplasmic asynchrony

Cytoplasm shows persistence of basophilia and may exhibit enlarged granules, hypogranulation, or agranularity

Nuclear asynchrony includes hypersegmentation or hyposegmentation

Clinical Conditions

- Myelodysplastic syndromes
- Some leukemias

Giant Myelocytes, Metamyelocytes, and Bands

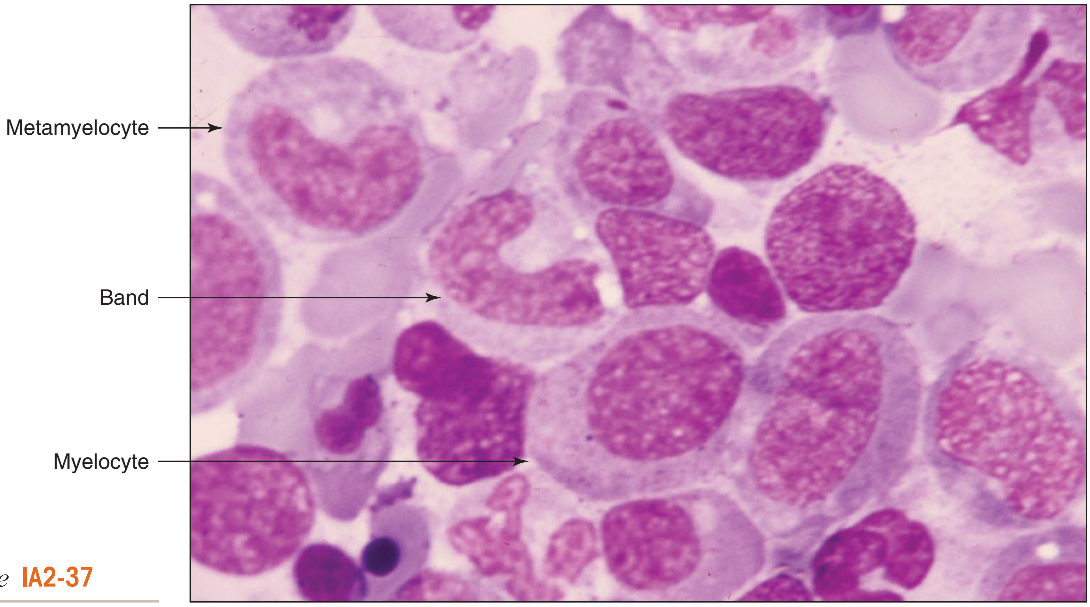


Figure **IA2-37**

Cell Type

Myelocyte, metamyelocyte, band

Description

Giant myelocytes are 17–26 μ; nucleus is round, oval, or flattened on one side, dark purple, coarse chromatin, and no visible nucleoli; cytoplasm is pinkish-blue with variable numbers of granules

Giant metamyelocytes are 15–22 μ; typical dark purple, kidney-shaped nucleus; cytoplasm is pink-blue with pinkish to reddish-blue granules

Giant bands are 14–20 μ; dark purple nucleus is band shaped; cytoplasm is pink-blue with pinkish-blue granules

Clinical Conditions

- Folate deficiency
- Vitamin B_{12} deficiency
- Chemotherapy (folate antagonists)

MONOCYTES

Monocyte Maturation Series

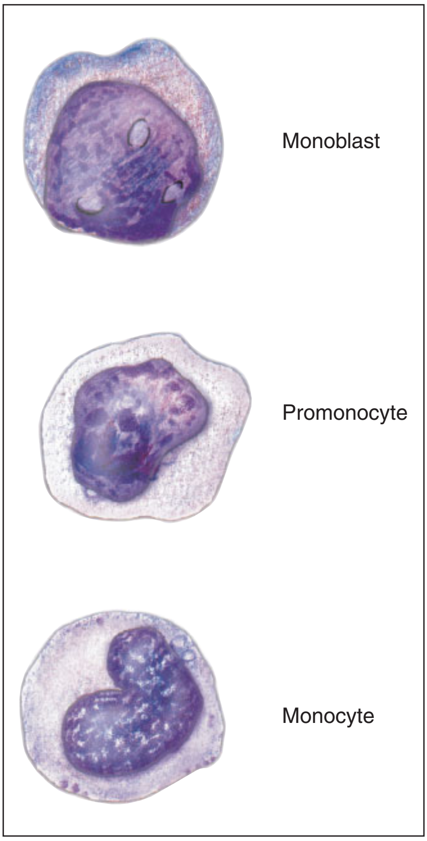

Monoblast
Promonocyte
Monocyte

Figure IA2-38

Monoblast

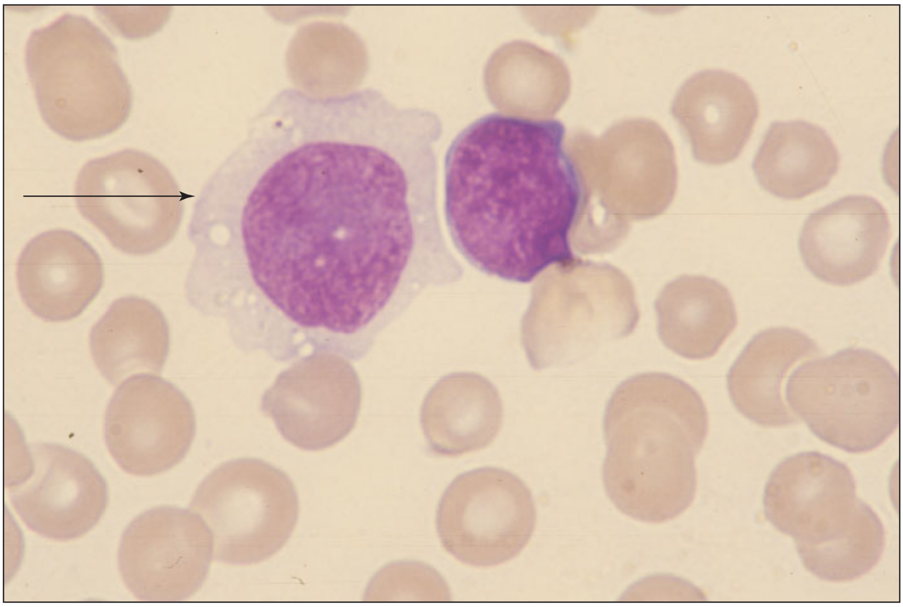


Figure IA2-39

Size: 14–20 μ

Nucleus

Shape: Round or oval
N/C Ratio: 3:1–1:1
Color: Light bluish-purple
Chromatin: Fine and distinct
Nucleoli: 1–5

Cytoplasm

Color: Blue-gray
Contents: No granules

Clinical Conditions

- Acute myelomonocytic leukemia (M4) (FAB)
- Acute monoblastic leukemia (M5a) (FAB)
- Acute monocytic leukemia (M5b) (FAB)
- Acute myelomonocytic leukemia (WHO)
- Acute monoblastic and monocytic leukemia (WHO)

Promonocyte

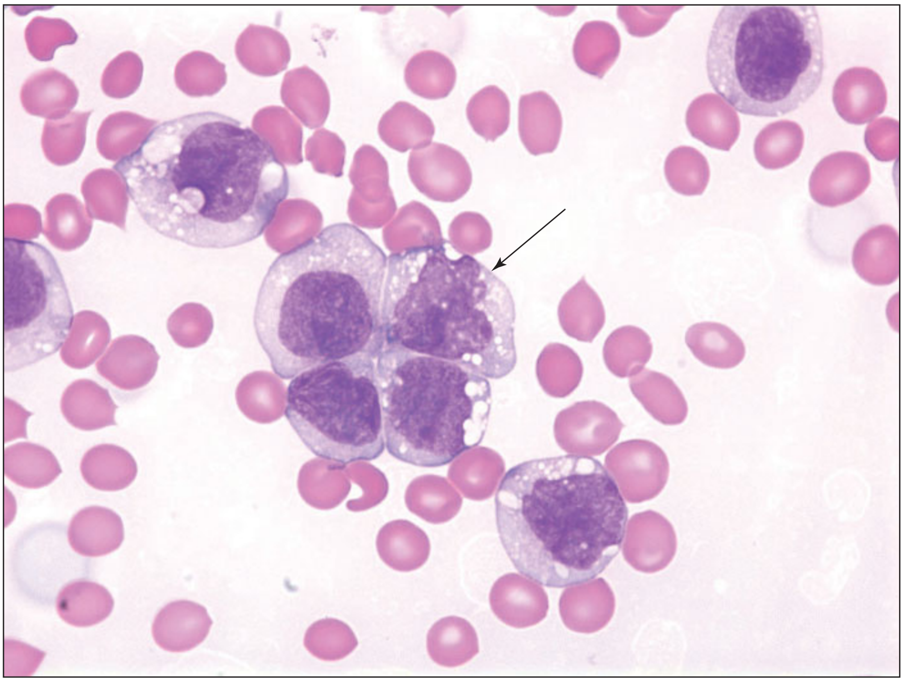


Figure IA2-40

Size: 14–20 μ

Nucleus

Shape: Oval or indented
N/C Ratio: 2:1–1:1
Color: Light bluish–purple
Chromatin: Fine reticular pattern
Nucleoli: 1–5

Cytoplasm

Color: Blue-gray, finely granular (ground glass) appearance
Contents: Many fine, dustlike, bluish granules; occasional vacuole

Clinical Conditions

- Acute myelomonocytic leukemia (M4) (FAB)
- Acute monoblastic leukemia (M5a) (FAB)
- Acute monocytic leukemia (M5b) (FAB)
- Myelodysplastic/myeloproliferative diseases—chronic myelomonocytic leukemia (CMML)
- Acute myelomonocytic leukemia (WHO)
- Acute monoblastic and monocytic leukemia (WHO)

Monocyte

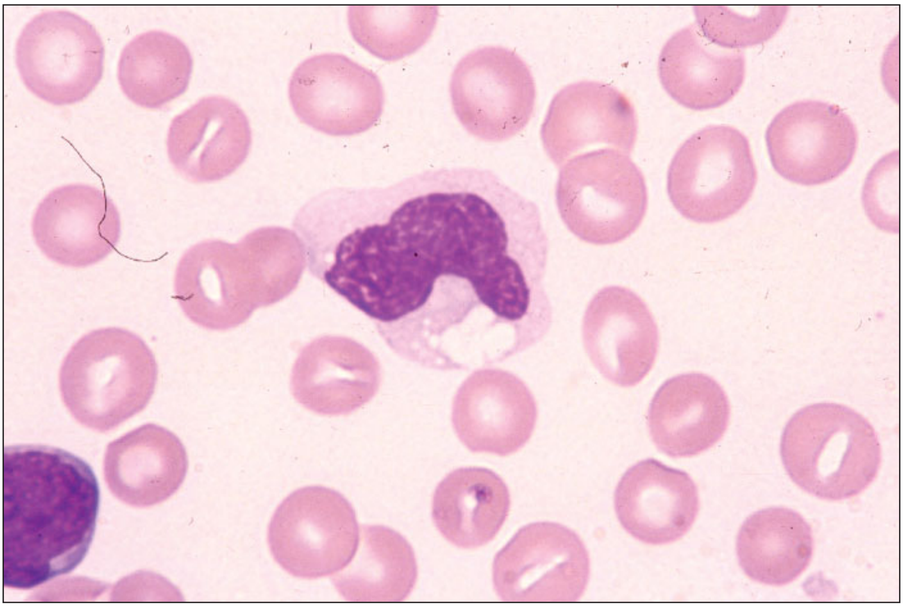


Figure IA2-41

Size: 14–21 µ

Nucleus

Shape: Horseshoe shaped or indented; nuclear folding may give the appearance of brainlike convolutions

N/C Ratio: 1:1

Color: Dark purple

Chromatin: Fine, delicate strands in linear arrangement with light spaces between strands

Nucleoli: None

Cytoplasm

Color: Blue-gray, finely granular (ground glass) appearance

Contents: Many fine, dustlike, bluish granules; occasional vacuole and blunt pseudopods

Clinical Conditions

- Myelodysplastic/myeloproliferative diseases—CMML, juvenile myelomonocytic leukemia (JMML)
- Myeloproliferative diseases—CML (few cases)
- Severe infections

LYMPHOCYTES

Lymphocyte Maturation Series

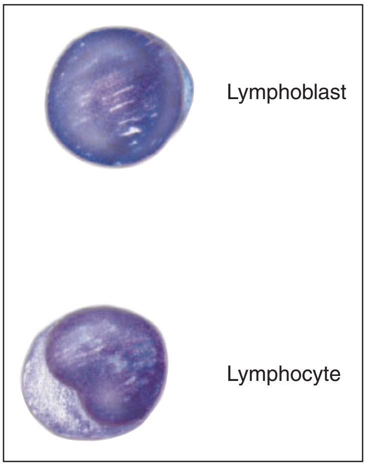

Lymphoblast
Lymphocyte

Figure IA2-42

Lymphoblast

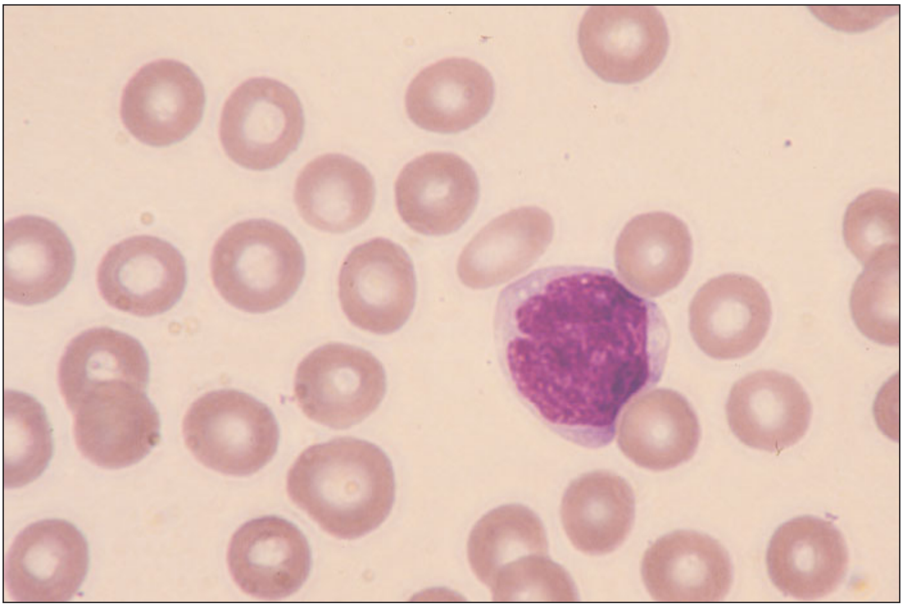


Figure IA2-43

Size: 10–22 µ

Nucleus

Shape: Round or oval, centrally or eccentrically placed
N/C Ratio: 7:1–4:1
Color: Reddish-purple
Chromatin: Fine, lacy pattern to moderately coarse
Nucleoli: 1–2 prominent

Cytoplasm

Color: Moderate to dark blue
Contents: Smooth, no granules, occasional vacuoles

Clinical Conditions

- Precursor lymphoblastic leukemia (L_1, L_2) (FAB)
- Burkitt lymphoma (L_3) (FAB)
- Lymphoblastic lymphoma

Mature Lymphocyte

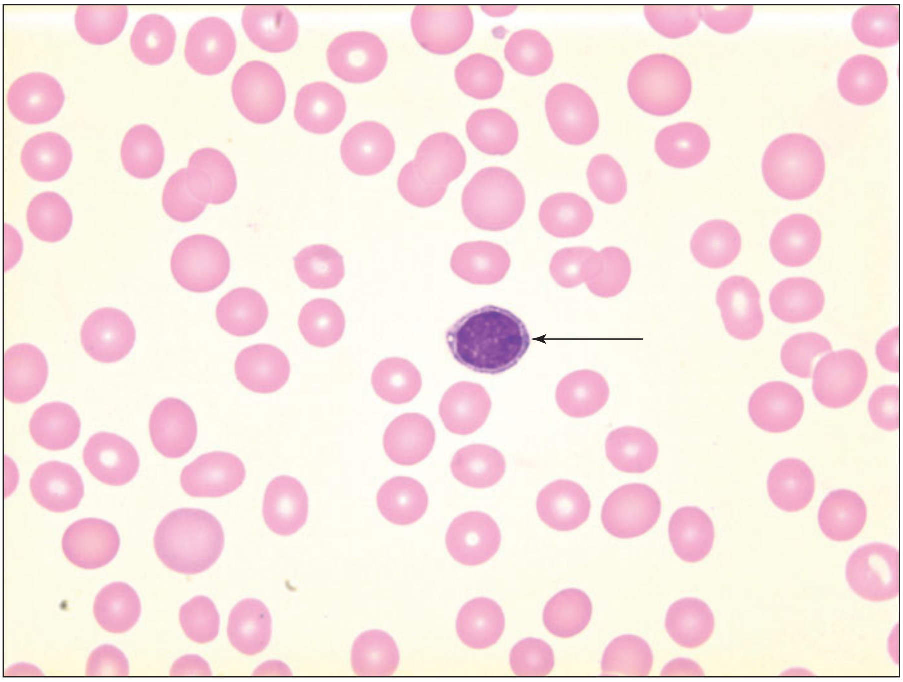


Figure IA2-44

Size: 7–15 μ

Nucleus

Shape: Round or slightly indented, eccentric
N/C Ratio: 3:1
Color: Deep purple–blue
Chromatin: Course and clumped
Nucleoli: None visible

Cytoplasm

Color: Sky blue to deep blue
Contents: Scant and usually nongranular; few azurophilic granules may be seen

♦ REACTIVE LYMPHOCYTES

Reactive Lymphocytes (Atypical Lymphocytes)

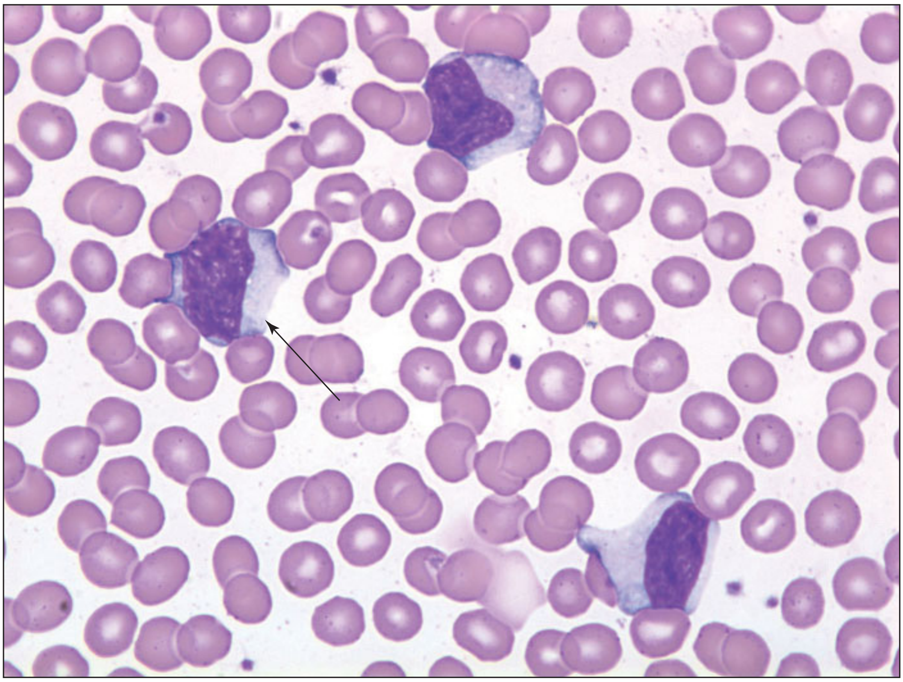


Figure IA2-45

Cell Type

Lymphocyte

Description

Cell size ranges from 10–25 μ
Nucleus can be oval, notched, indented, or elongated
One or more large nucleoli may be visible
Cytoplasm is often abundant and stains pale to deep blue and darker at periphery; may be partially indented by adjacent red cells; few lavender granules and/or vacuoles

Clinical Conditions

- Infectious mononucleosis
- Other viral diseases including cytomegalovirus, toxoplasmosis, hepatitis, and cat scratch fever

Cleaved Cell (Butt Cell)

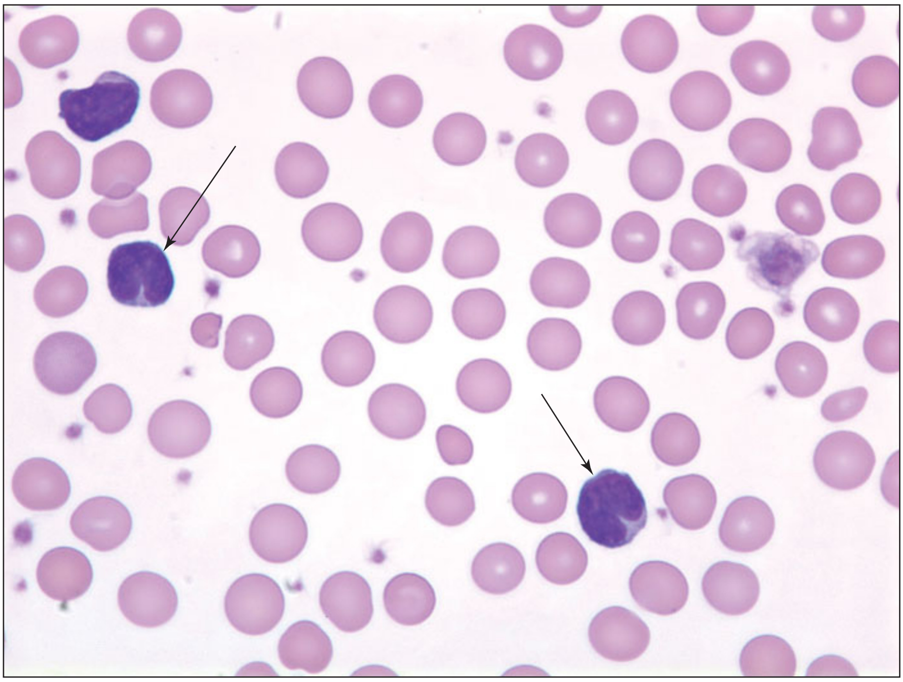


Figure IA2-46

Cell Type

Lymphocyte

Description

Small, mature lymphocyte with cleaved nucleus

Clinical Conditions

- Pertussis (Whooping cough)
- Lymphoma
- Chronic lymphocytic leukemia

Immunoblast

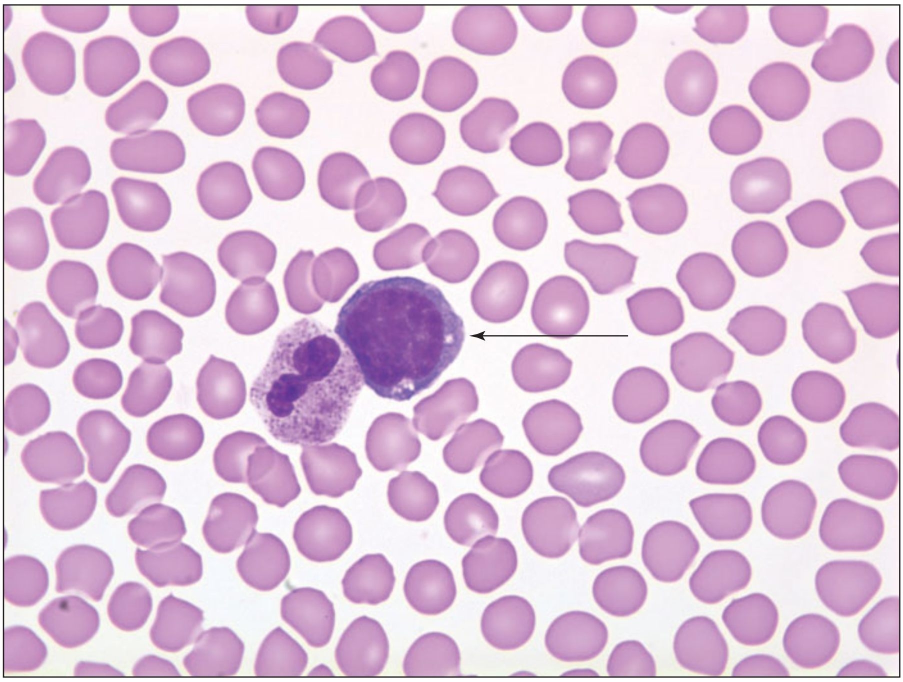


Figure **IA2-47**

Cell Type

Lymphocyte

Description

Large cell (12–25 μ) with bluish-purple nucleus and fine chromatin pattern with several prominent nucleoli

Cytoplasm is deep blue

Clinical Conditions

- Viral and nonviral infections
- Immune disorders

Large Granular Lymphocyte

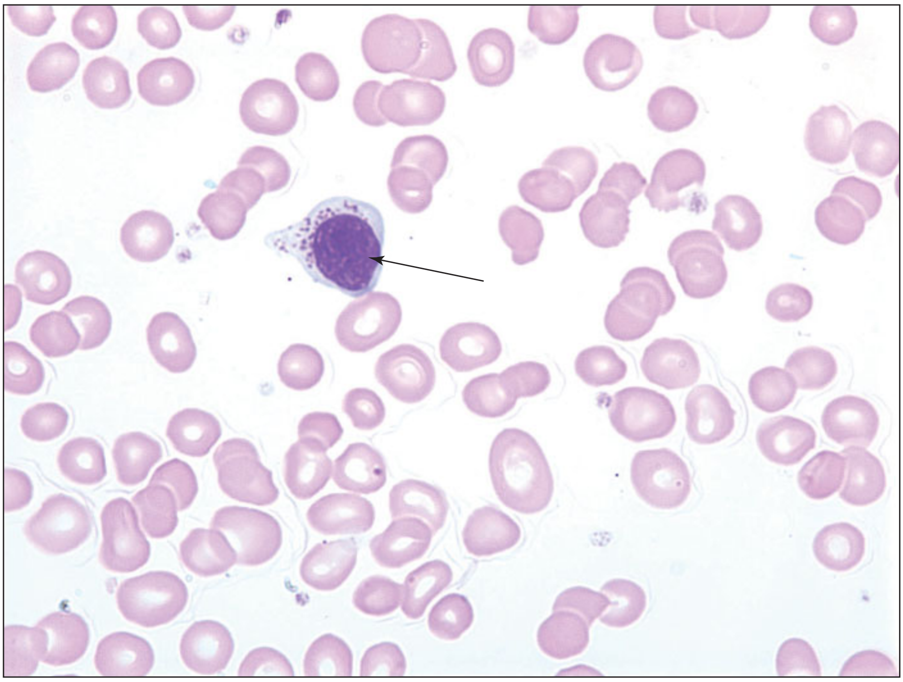


Figure IA2-48

Cell Type

Lymphocyte

Description

Large cells (14–16 μ) with moderate to abundant pale blue cytoplasm
Prominent azurophilic granules

Clinical Conditions

- T-gamma lymphoproliferative disease
- Large granular lymphocytic leukemia
- NK cell leukemia

Large Lymphocyte

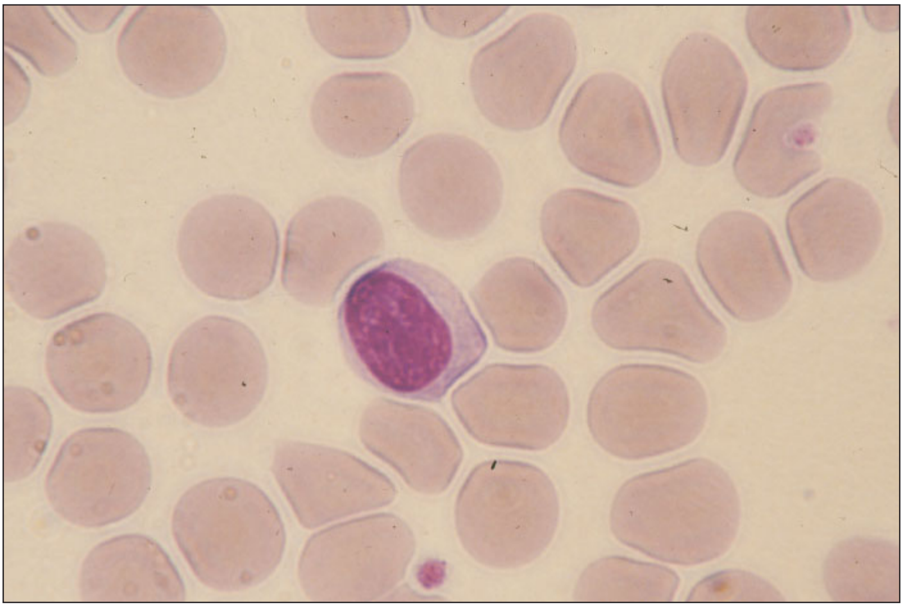


Figure **IA2-49**

Cell Type

Lymphocyte

Description

Nucleus is round or oval, may be slightly indented, with coarse chromatin pattern and no visible nucleoli; moderate, pale-blue cytoplasm with rare purplish-red granules

Clinical Condition

- 10–12% of lymphocytes is normal

Plasmacytoid Lymphocyte

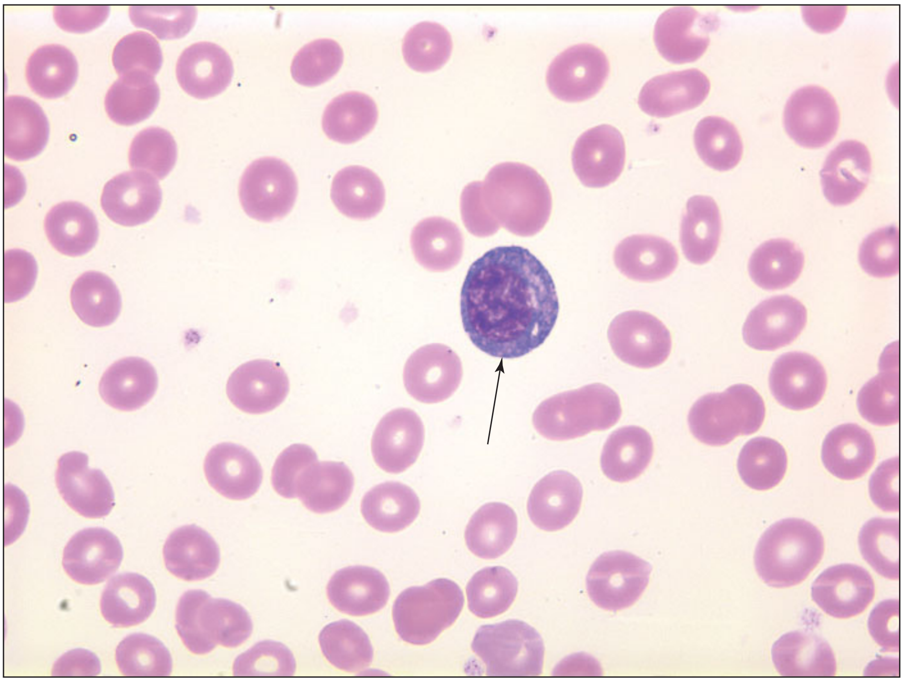


Figure **IA2-50**

Cell Type

Lymphocyte

Description

Cell is intermediated between small lymphocyte and plasma cell (9–20 μ); nucleus is centrally to slightly eccentrically located, indented or oval, with a developing perinuclear halo; chromatin strands are heavy or in dense blocks; cytoplasm is intensely basophilic and may contain few vacuoles

Clinical Conditions

- Viral and nonviral infections
- Immune disorders
- Plasma cell myeloma
- Waldenström macroglobulinemia

MALIGNANT LYMPHOCYTES

Chronic Lymphocytic Leukemia Lymphocyte

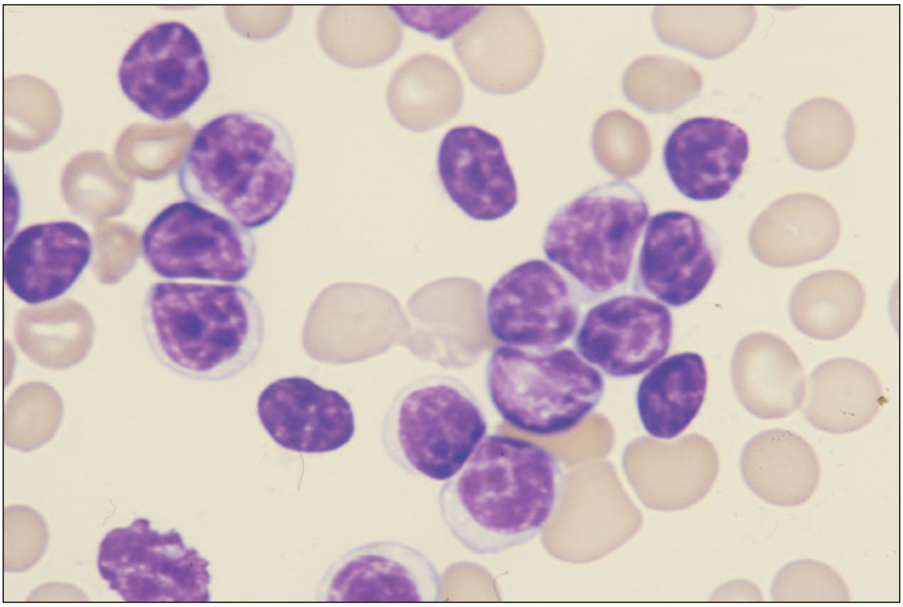


Figure IA2-51

Cell Type

Lymphocyte

Description

Cell size ranges from 10–15 μ
Nucleus is round, with an N/C ratio of 7:1–3:1
Chromatin is clumped and may show a compartmentalization phenomenon
Nucleoli are inconspicuous or not visible
Cytoplasm is sparse to abundant, clear, and lightly basophilic

Clinical Conditions

- Chronic lymphocytic leukemia
- Prolymphocytic leukemia/chronic lymphocytic leukemia
- Prolymphocytic leukemia

Hairy Cell

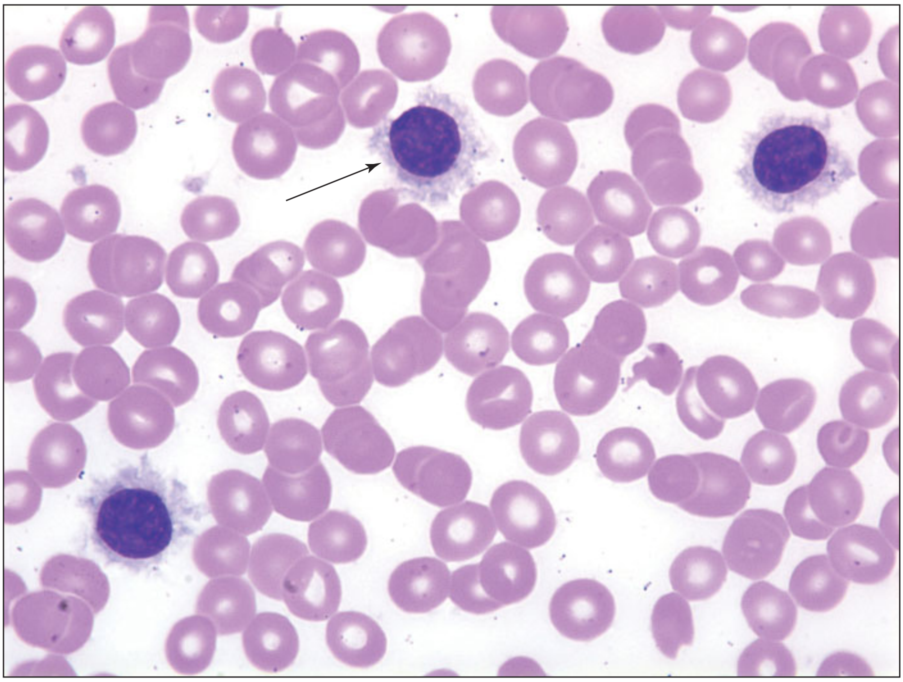


Figure IA2-52

Cell Type

Lymphocyte

Description

Scant to abundant agranular, light grayish–blue cytoplasm; numerous, irregular cytoplasmic projections give a hairlike or ruffled appearance to plasma membrane; nucleus is round or oval and may occasionally appear kidney or hourglass shaped; loose and lacy chromatin pattern with one or two visible nucleoli

Clinical Condition

- Hairy cell leukemia

L_1 Lymphoblast (FAB)

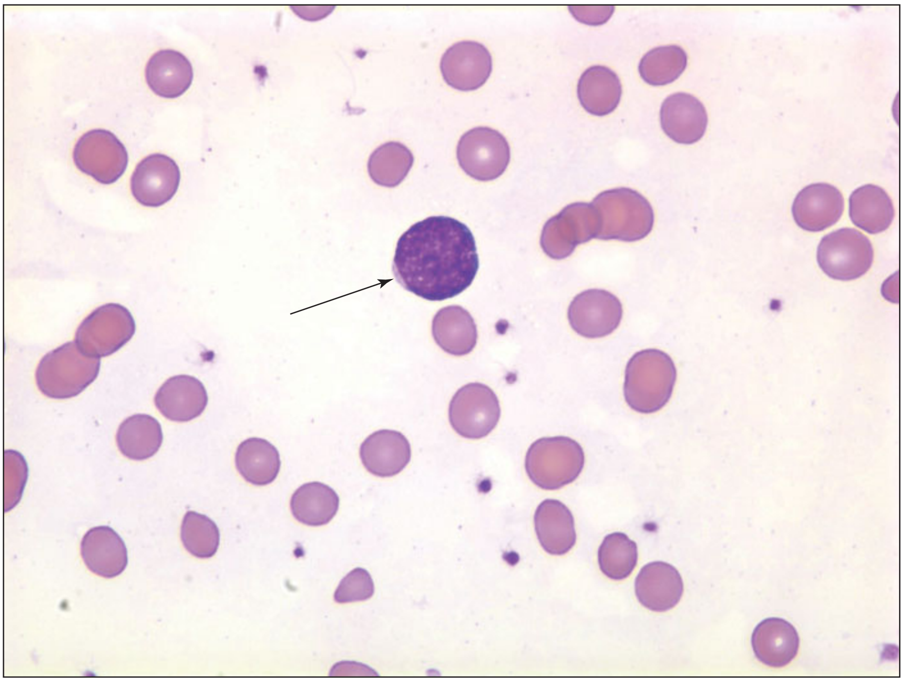


Figure IA2-53

Cell Type

Lymphoblast

Description

Cell size ranges from 10–14 μ
Nuclear shape is regular or small cleaved and indented
Purple nucleus has a homogeneous and condensed chromatin pattern
Nucleoli are inconspicuous or not visible (0-1)
Scanty cytoplasm is moderately basophilic and rarely vacuolated

Clinical Condition

- Precursor lymphoblastic leukemia

L_2 Lymphoblast (FAB)

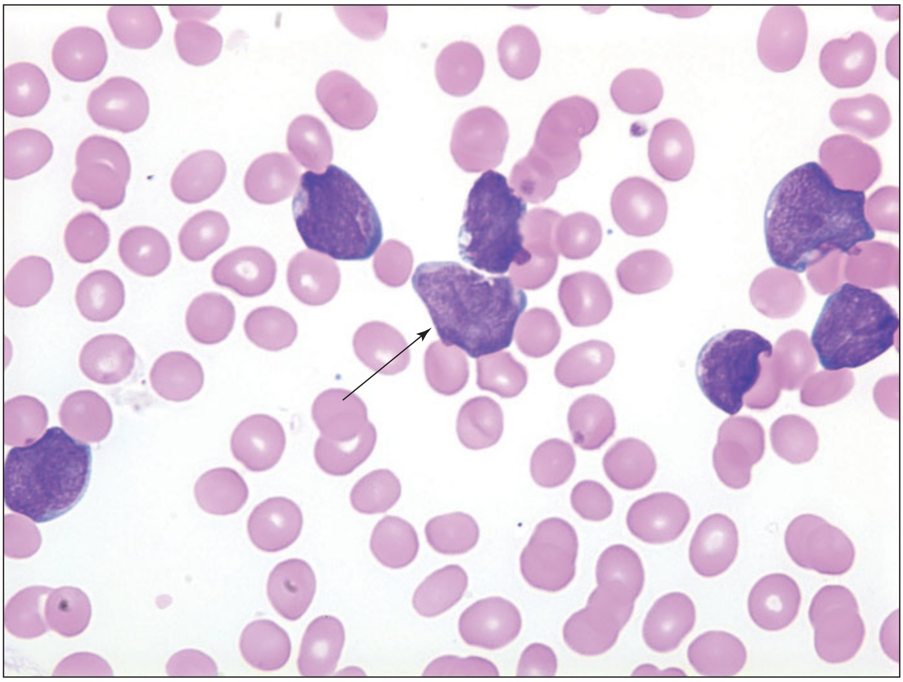


Figure **IA2-54**

Cell Type

Lymphoblast

Description

Cell size ranges from 14–22 μ
Nucleus has an irregular or indented shape
N/C ratio is average (4:1)
Nucleus is purplish-red, with variable heterogeneous chromatin
One to two nucleoli are often prominent
Cytoplasm is variable but occasionally intensely basophilic and rarely vacuolated

Clinical Condition

- Precursor lymphoblastic leukemia

L_3 Lymphoblast (FAB)

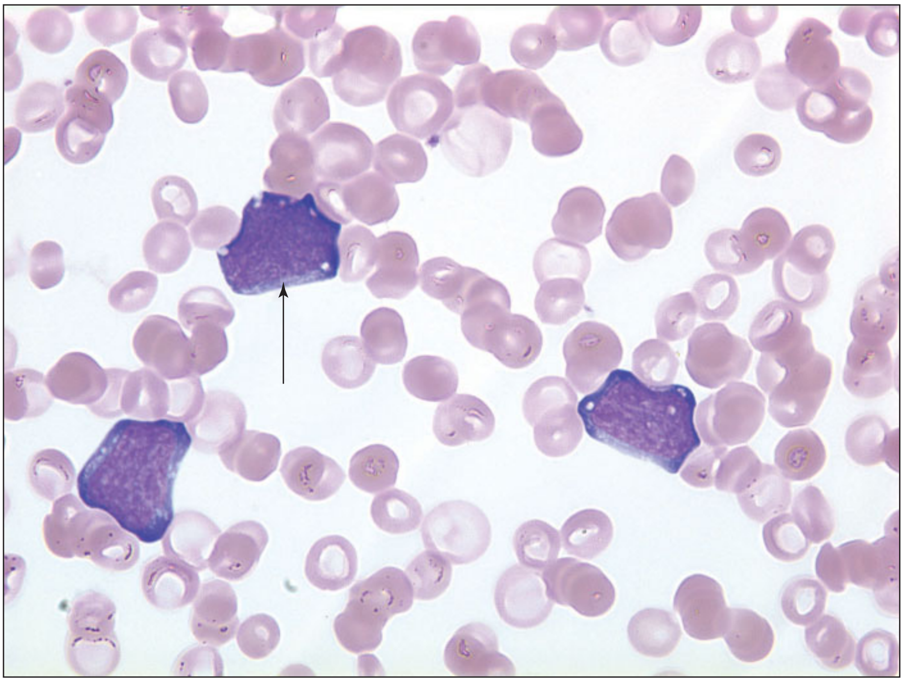


Figure **IA2-55**

Cell Type

Lymphoblast

Description

Cell size ranges from 14–18 μ

Nucleus is oval to round, purple, and has a finely stippled and homogeneous chromatin pattern

N/C ratio is 5:1–4:1

One to two nucleoli are often prominent

Cytoplasm is intensely basophilic with prominent vacuolization

Clinical Conditions

- Burkitt lymphoma
- Acute lymphoblastic leukemia (L_3) (FAB)
- Burkitt leukemia/lymphoma (WHO)

Prolymphocyte

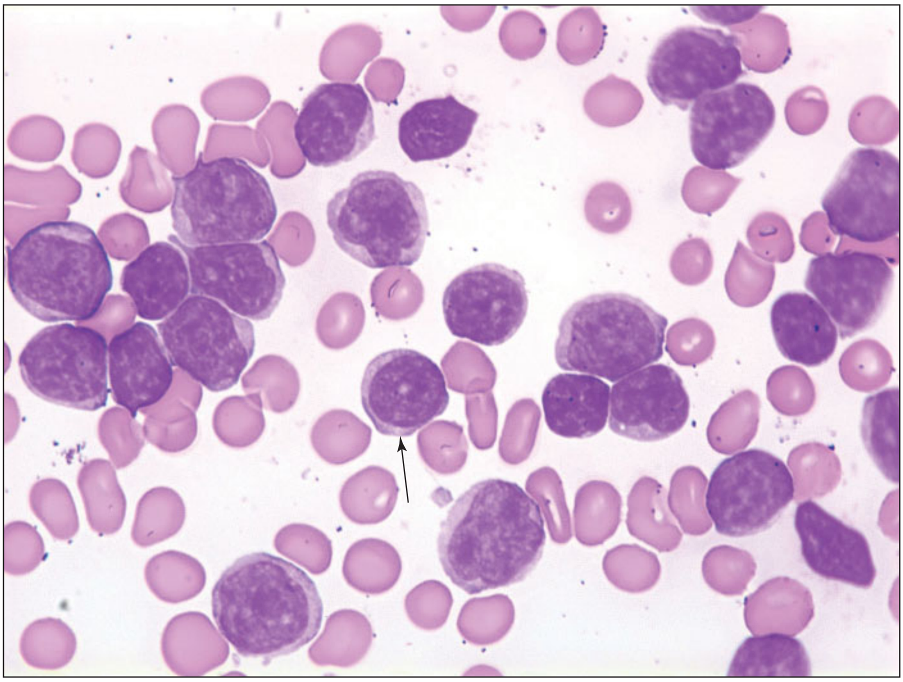


Figure IA2-56

Cell Type

Lymphocyte

Size: 10–15 μ

Description

Round, centrally placed nucleus that is reddish-purple, with coarse, clumped chromatin

N/C ratio is 3:1–4:1

One prominent nucleolus

Cytoplasm is abundant; light to moderate blue

Clinical Conditions

- Chronic lymphocytic leukemia (<11% prolymphocytes) (FAB)
- Prolymphocytic leukemia (>55% prolymphocytes) (FAB)
- Chronic lymphocytic leukemia/prolymphocytic leukemia (11–55% prolymphocytes) (FAB)
- B cell prolymphocytic leukemia (>55% prolymphocytes) (WHO)

LYMPHOMA CELLS

Lymphoblastic Lymphoma Cell

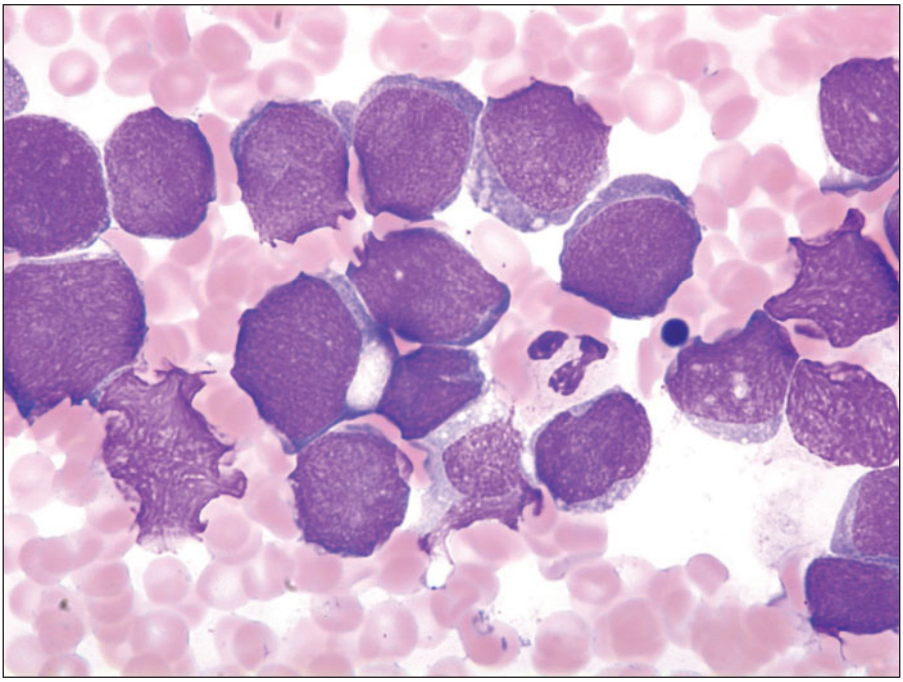


Figure IA2-57

Cell Type

Lymphoblast

Description

Cell size is variable
Nucleus is indented or convoluted, with fine chromatin pattern and small, inconspicuous nucleoli
Cytoplasm is scant

Clinical Condition

- Lymphoblastic lymphoma

Reed-Sternberg Cell

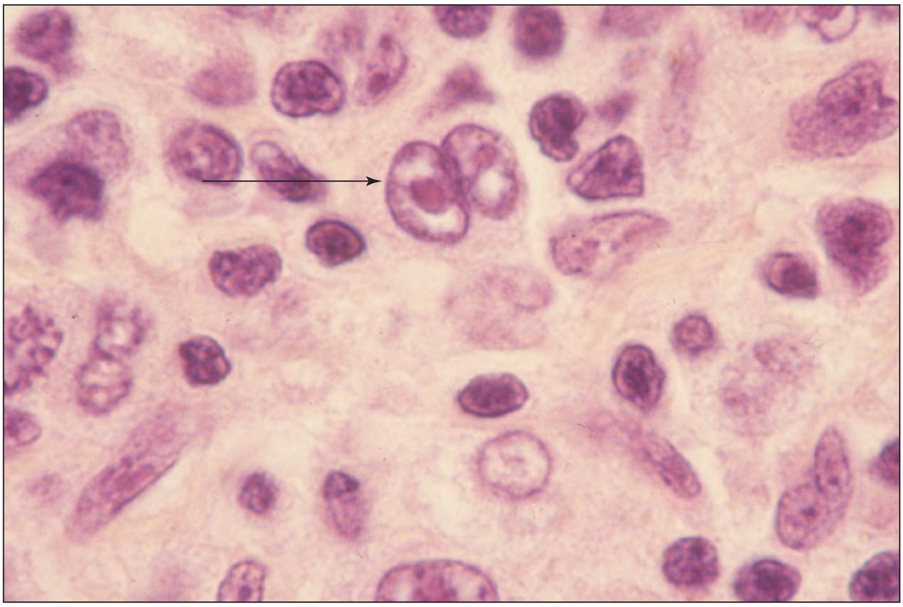


Figure **IA2-58**

Cell Type

Lymphocytic lineage

Description

A large cell (50–100 μ) with an abundance of cytoplasm

Nucleus is often bilobed or binucleated, with prominent large nucleoli resembling owl eyes; the two halves of a binucleated cell often appear as mirror images

Not found in peripheral blood; found in lymph nodes

Clinical Condition

- Hodgkin lymphoma

Sézary Cell

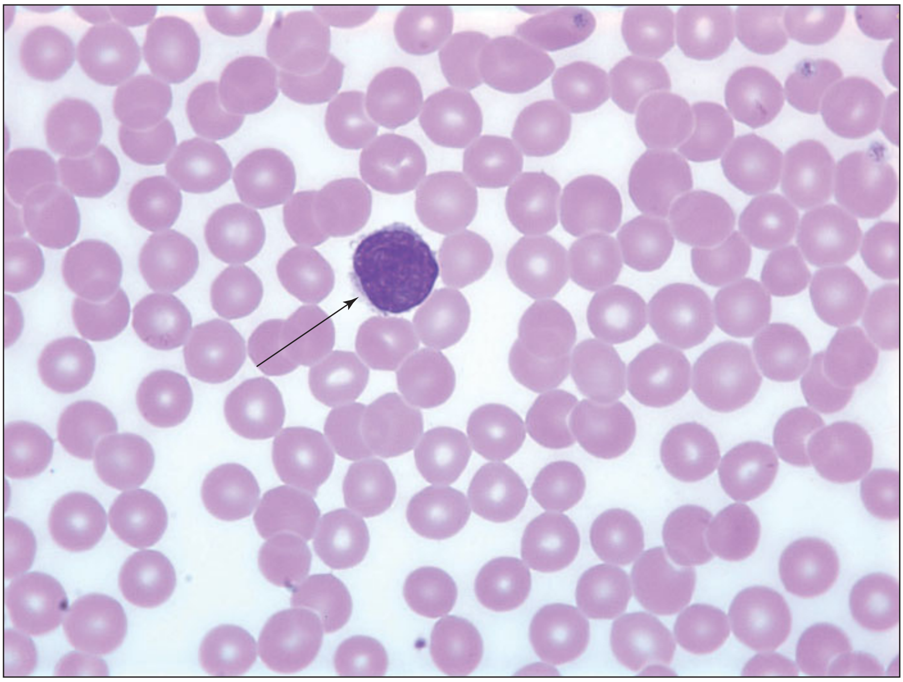


Figure **IA2-59**

Cell Type

Lymphocyte

Description

Small and large cell ranging from 8–30 μ

Nucleus has brainlike convolutions and is dark purple, with moderately coarse chromatin; nucleoli are not visible

Cytoplasm is scanty and pale to deep blue with occasional vacuoles

Clinical Conditions

- Cutaneous T-cell lymphoma (mycosis fungoides, Sézary syndrome)
- T_4 lymphomas involving the skin

Small Cleaved Lymphoma Cell

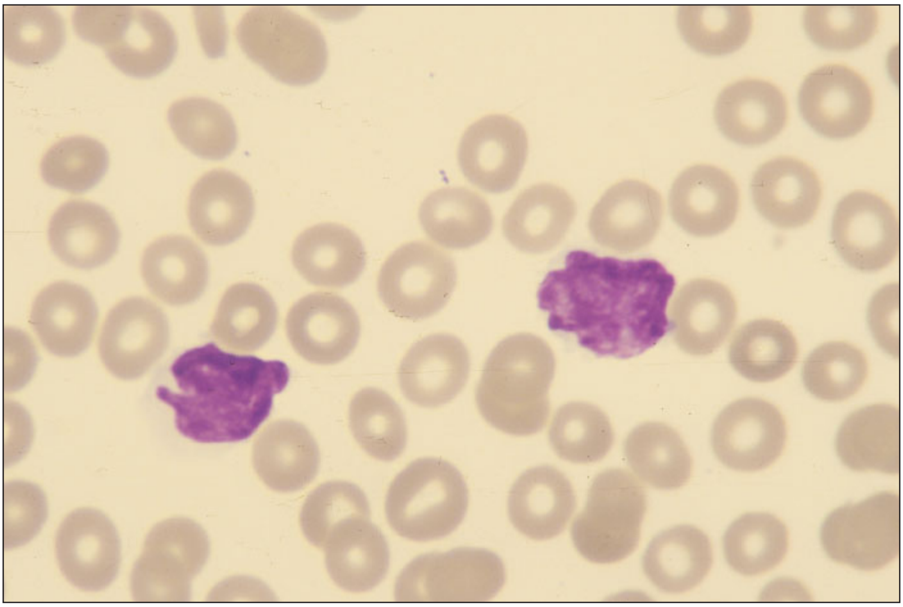


Figure **IA2-60**

Cell Type

Lymphoma cell

Description

Cell size is 6–12 μ; nucleus is twisted, angulated, and indented, with clumped chromatin and no nucleoli

Cytoplasm is scant to imperceptible

Clinical Condition

- Small cleaved cell lymphoma

Small B Lymphoma Cell

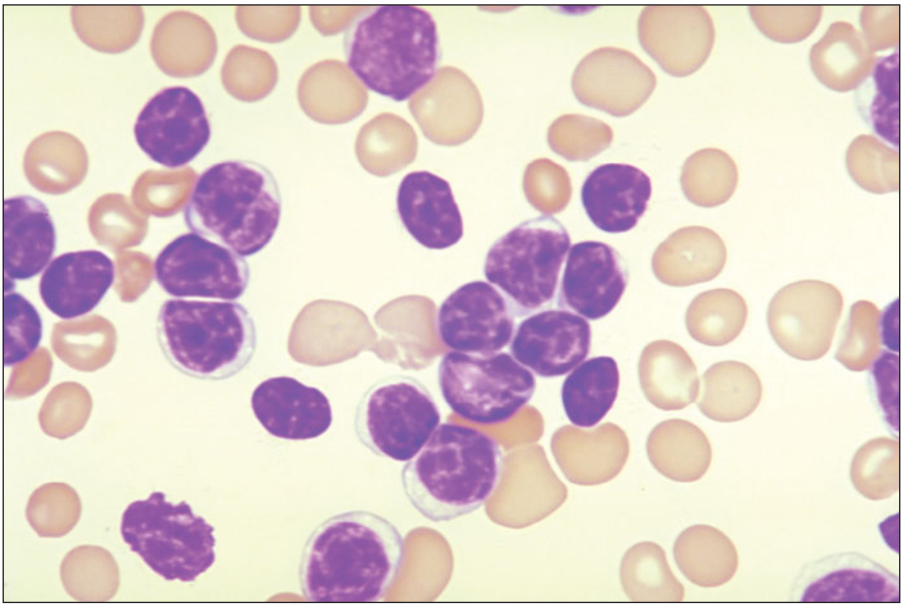


Figure IA2-61

Cell Type

Lymphocyte

Description

Cell is 10–25 μ; round nucleus has clumped chromatin and may show a compartmentalization phenomenon

Nucleoli are inconspicuous or not visible

Cytoplasm is sparse to abundant and clear and lightly basophilic

Clinical Condition

- Lymphoma

PLASMACYTES

Plasma Cell Series

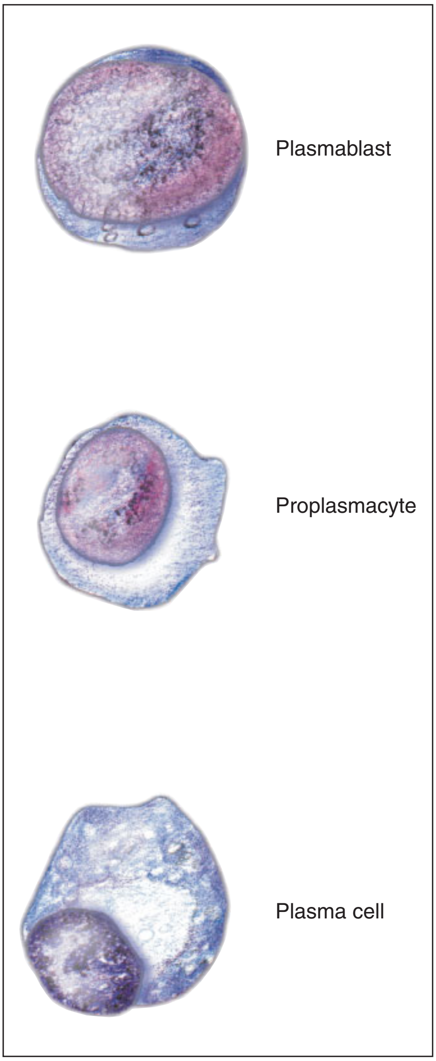

Plasmablast
Proplasmacyte
Plasma cell

Figure IA2-62

Plasmablast

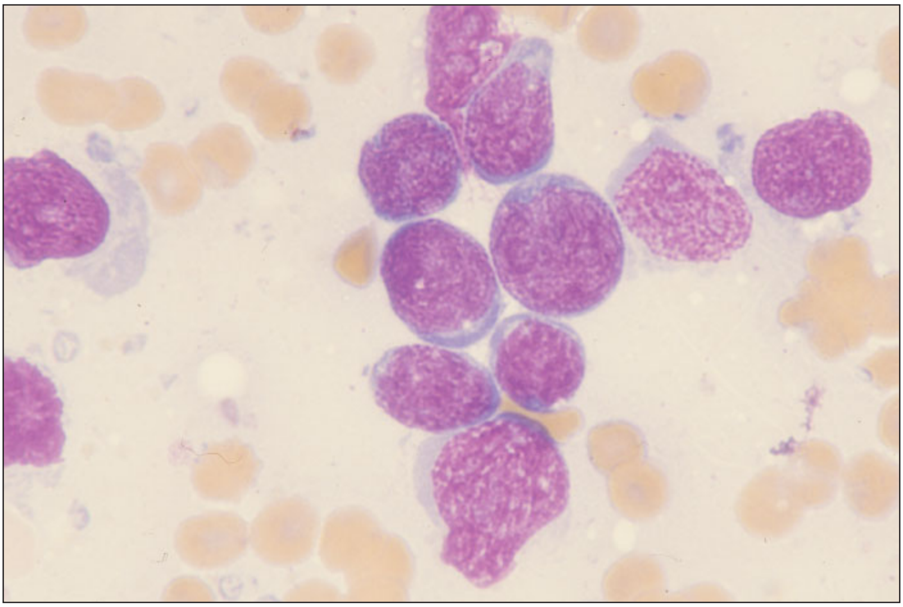


Figure IA2-63

Size: 12–15 μ

Nucleus

Shape: Round
N/C Ratio: 5:1–4:1
Color: Purplish-red
Chromatin: Fine and linear strands
Nucleoli: 1–2

Cytoplasm

Color: Blue
Contents: Nongranular

Clinical Conditions

- Plasma cell leukemia
- Plasma cell myeloma

Proplasmacyte

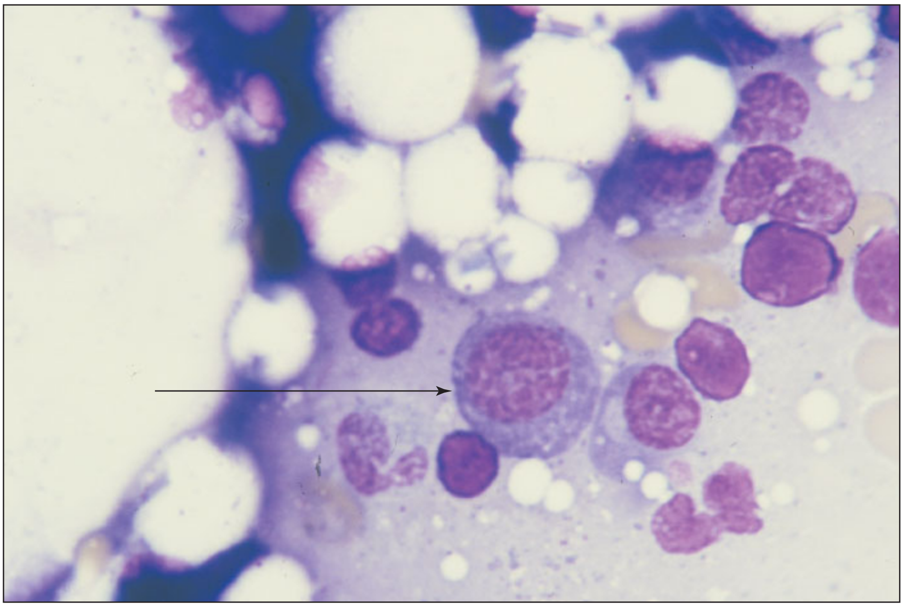


Figure **IA2-64**

Size: 12–15 μ

Nucleus

Shape: Round, eccentrically placed
N/C Ratio: 5:1–4:1
Color: Purplish-red
Chromatin: Moderately clumped
Nucleoli: 0–2

Cytoplasm

Color: Dark blue, prominent light area next to nucleus
Contents: Nongranular

Clinical Conditions

- Plasma cell leukemia
- Plasma cell myeloma
- Waldenström macroglobulinemia
- Response to infection

Plasma Cell

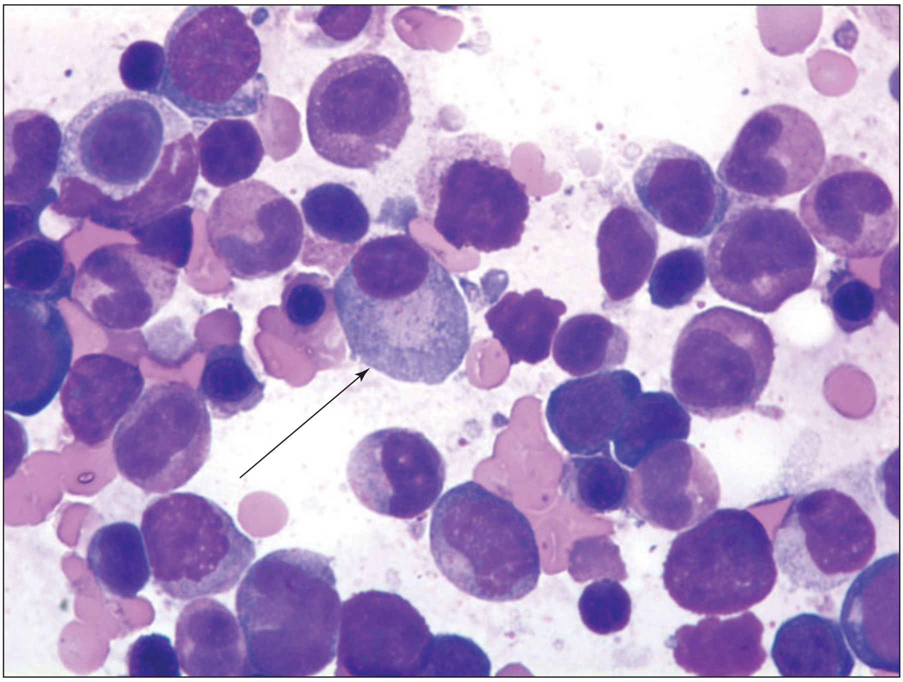


Figure IA2-65

Cell Type

Plasma cell

Description

Size ranges from 9–20 μ

Dark purple nucleus is ovoid and eccentrically placed, with a wheel-spoke pattern

No nucleoli

Cytoplasm is abundant and deep blue with a clear area next to the nucleus

Clinical Conditions

- Plasma cell dyscrasias
- Response to infections

ABNORMAL PLASMA CELLS AND INCLUSIONS

Bilobed Plasma Cell

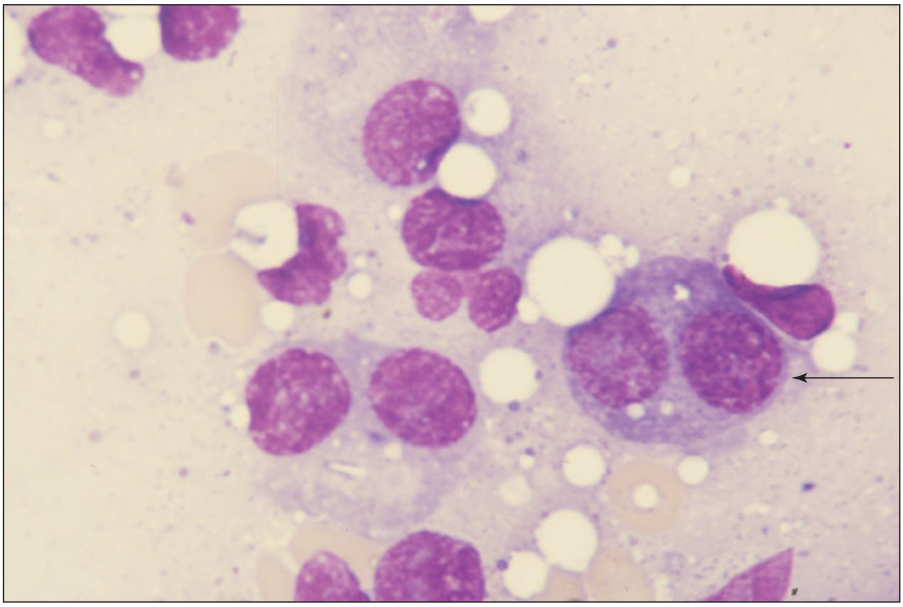


Figure **IA2-66**

Cell Type

Plasma cell

Description

Dark purple nucleus is bilobed rather than ovoid
Cytoplasm is pale to deeply basophilic

Clinical Condition

- Plasma cell dyscrasias

Dutcher Body

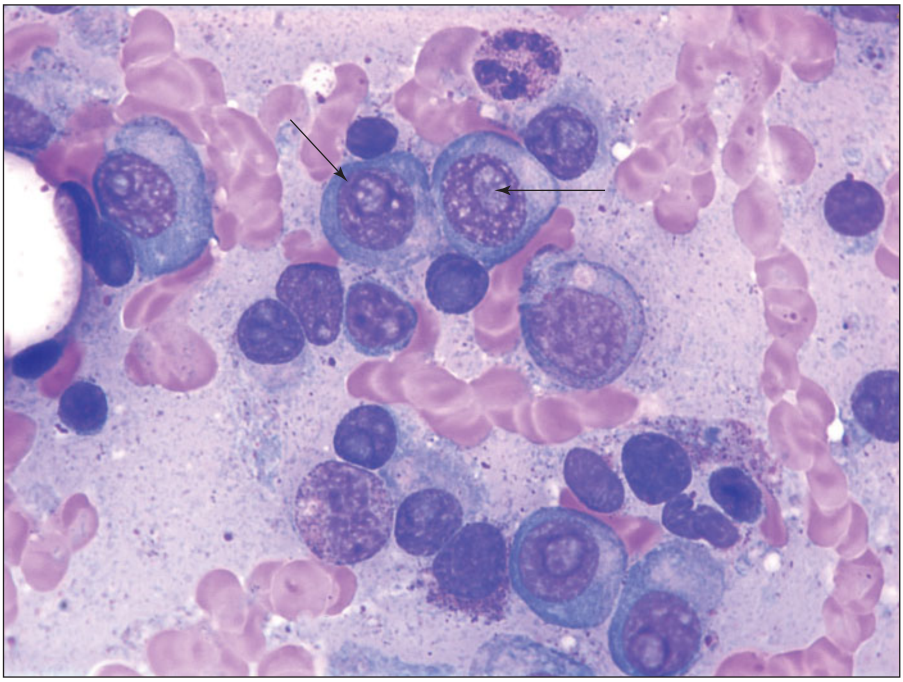


Figure IA2-67

Cell Type

Plasma cell

Description

Intranuclear protein inclusions resulting from membrane-bound cytoplasm in the nucleus

Clinical Condition

- Plasma cell dyscrasias

Flaming Plasma Cell

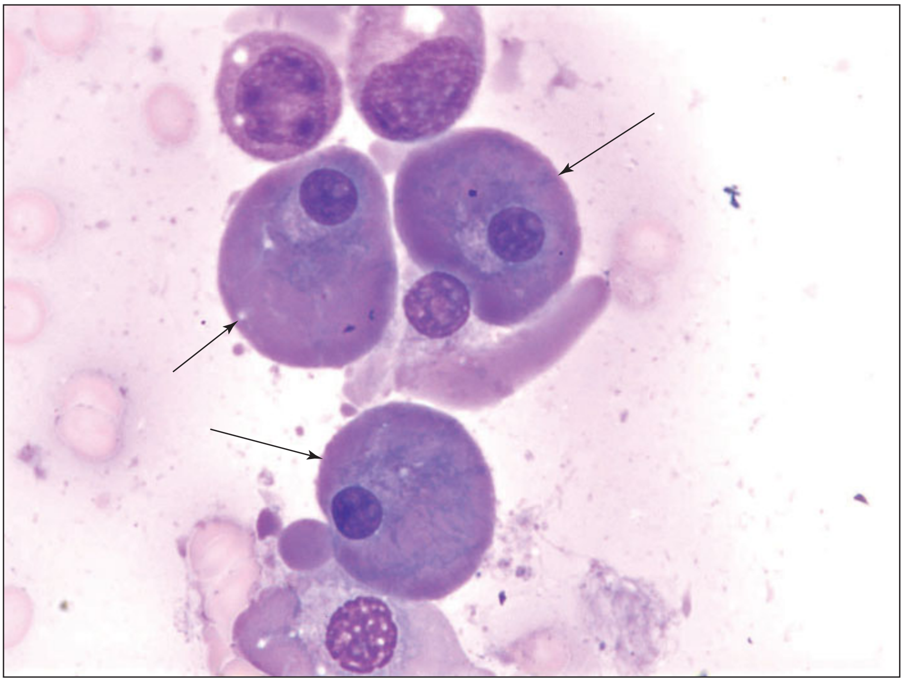


Figure **IA2-68**

Cell Type

Plasma cell

Description

Cytoplasmic immunoglobulin (often IgA) accumulating in the peripheral cytoplasm; stains reddish-purple

Clinical Condition

- Plasma cell dyscrasias

Mott Cell (Grape Cell)

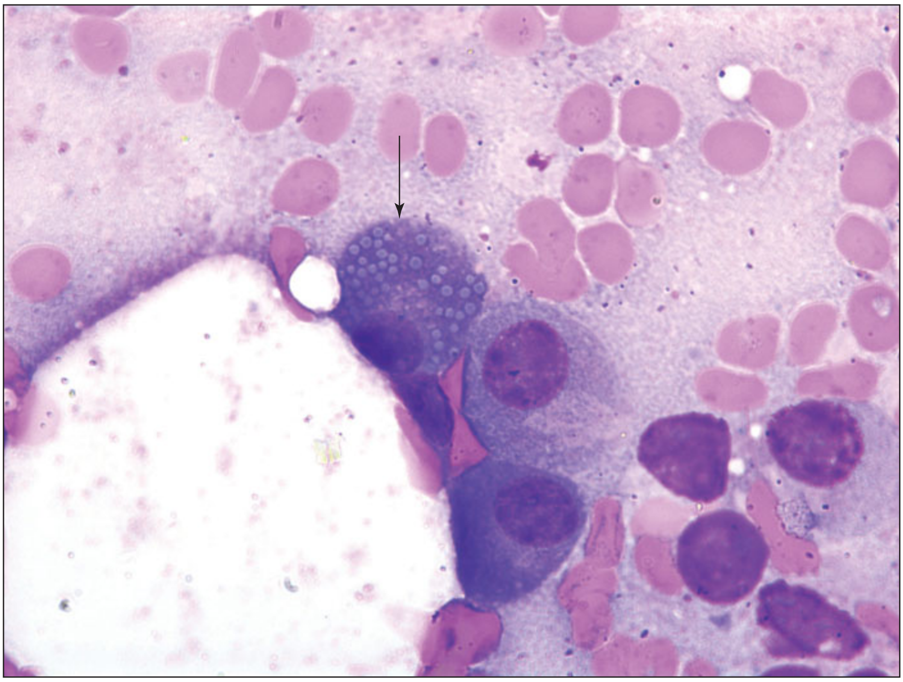


Figure IA2-69

Cell Type

Plasma cell

Description

Cytoplasm filled with Russell bodies resembling clusters of grapes

Clinical Condition

- Plasma cell dyscrasias

Russell Bodies

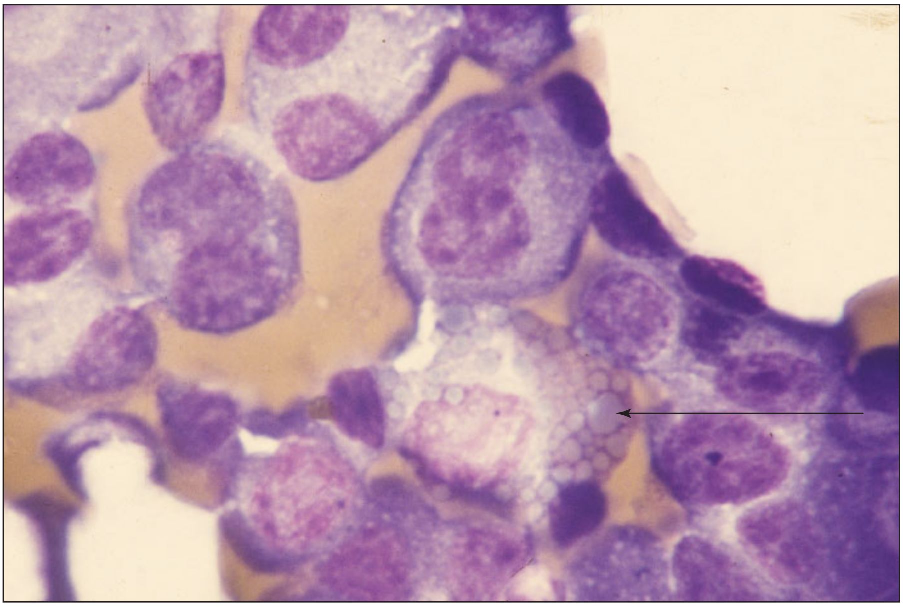


Figure IA2-70

Cell Type

Plasma cell

Description

Individual globules of immunoglobulin in cytoplasm, which represent rough endoplasmic reticulum, smooth endoplasmic reticulum, and Golgi filled with immunoglobulin due to secretory obstruction; globules stain pink or blue depending on pH; if immunoglobulin disappears, colorless vacuoles result

Clinical Condition

- Plasma cell dyscrasias

CHAPTER 3

Megakaryocytes

NORMAL MEGAKARYOCYTIC MATURATION SERIES

Normal Megakaryocytic Series

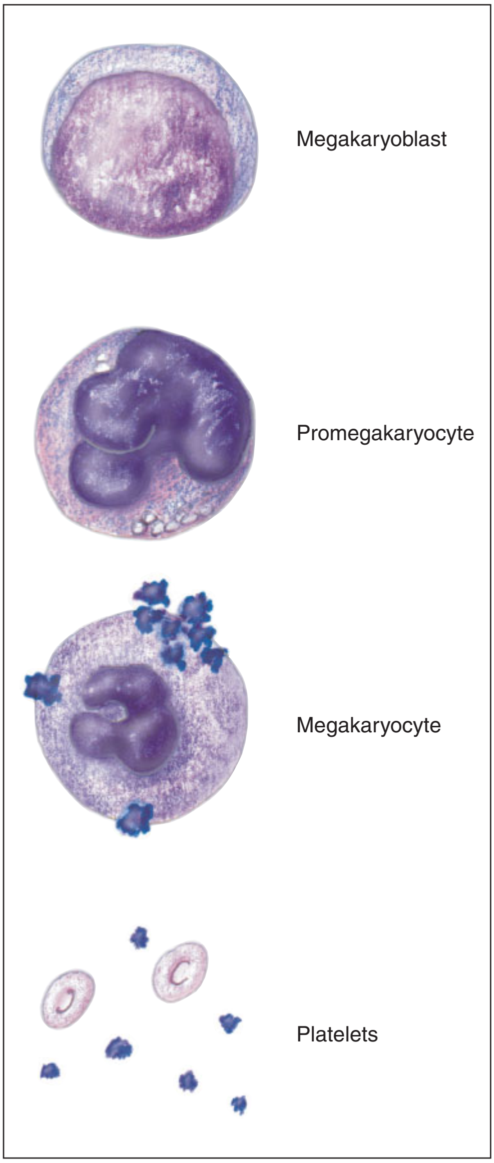

Megakaryoblast
Promegakaryocyte
Megakaryocyte
Platelets

Figure IA3-1

Megakaryoblast

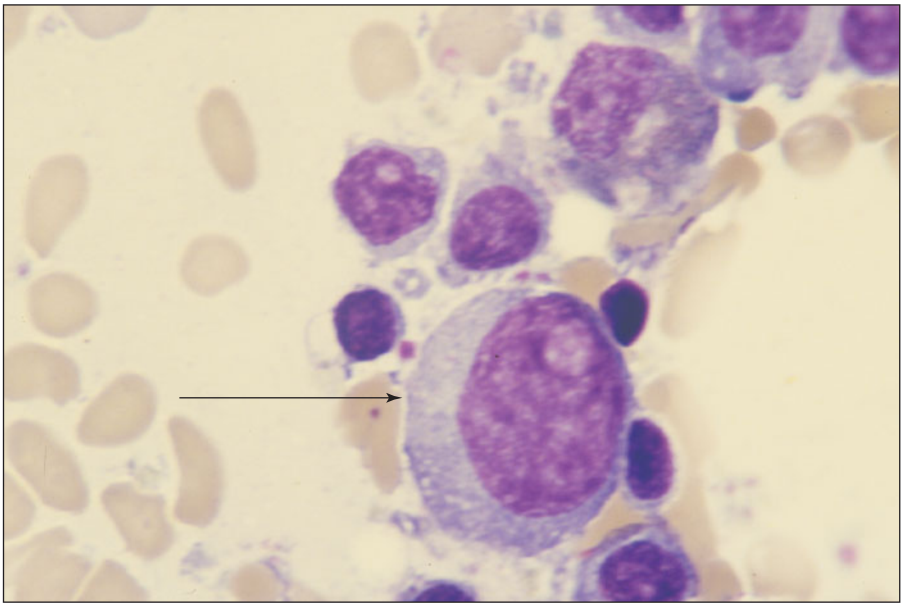


Figure IA3-2

Size: 20–50 μ

Nucleus

Shape: Round, oval, or kidney shaped
N/C Ratio: 5:1–3:1
Color: Reddish-purple to purple
Chromatin: Fine, distinct strands to dense chromatin
Nucleoli: Several, often indistinct or maybe more distinct in larger blasts

Cytoplasm

Color: Moderate to dark blue
Contents: Blunt cytoplasmic extensions; no granules to fine azurophilic granules in the larger blasts

Clinical Conditions

- Acute megakaryoblastic leukemia (M7) (FAB)
- Myeloproliferative diseases—CML, PMF
- Myelodysplastic syndromes
- Acute megakaryoblastic leukemia (WHO)

Promegakaryocyte

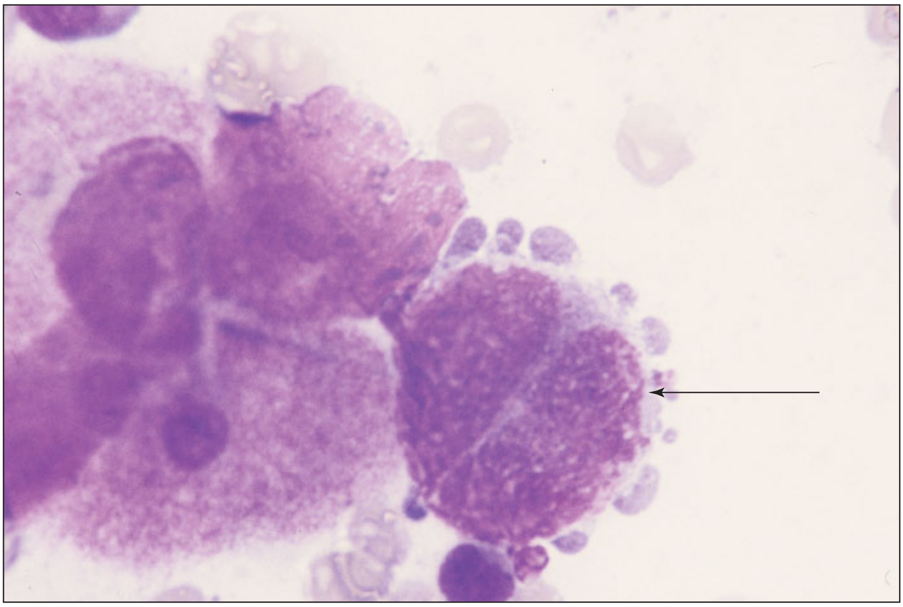


Figure IA3-3

Size: 20–80 µ

Nucleus

Shape: Irregularly indented, with 2–4 lobes
N/C Ratio: 1:1
Color: Dark purple
Chromatin: Fine; condensed near periphery
Nucleoli: Several

Cytoplasm

Color: Moderate blue to pinkish-blue
Contents: Few bluish granules; development of demarcation membrane system forming small cytoplasmic extensions

Clinical Conditions

- Acute megakaryoblastic leukemia (M7) (FAB)
- Myeloproliferative diseases—CML, PMF, essential thrombocytosis (ET)
- Myelodysplastic syndromes
- Acute myelocytic leukemia with multilineage dysplasia
- Acute megakaryoblastic leukemia (WHO)

Megakaryocyte

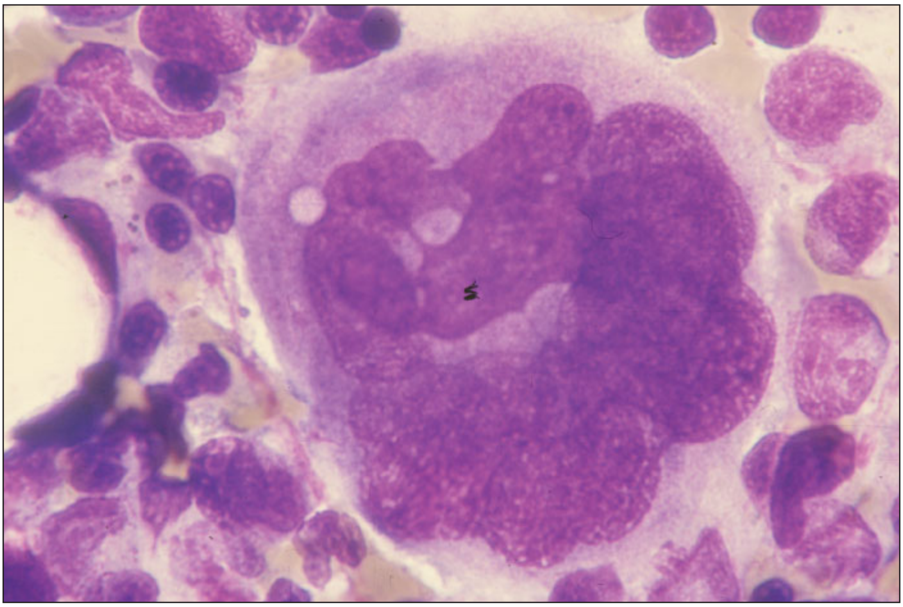


Figure IA3-4

Size: 40–100 μ

Nucleus

Shape: Multilobular
N/C Ratio: 1:1–1:12
Color: Dark purple
Chromatin: Coarse, linear
Nucleoli: None

Cytoplasm

Color: Pinkish-blue
Contents: Numerous reddish-blue granules

Clinical Conditions

- Myeloproliferative diseases—CML, PMF, ET
- Myelodysplastic syndromes
- Acute myelocytic leukemia with multilineage dysplasia

Platelets

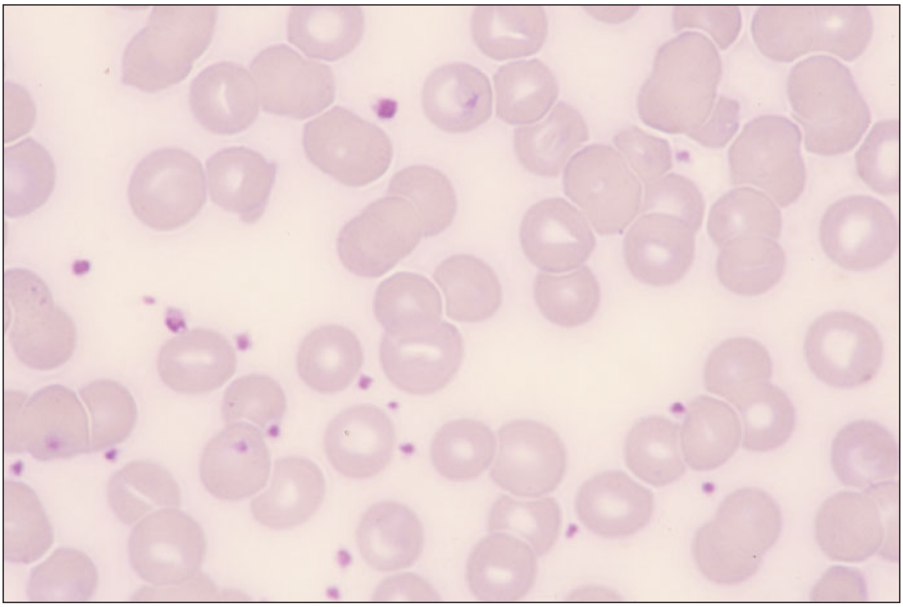


Figure IA3-5

Size: 1–4 μ

Nucleus

None

Cytoplasm

Color: Light blue
Contents: Small reddish-blue granules

ABNORMAL MEGAKARYOCYTIC CELLS

Giant Platelet

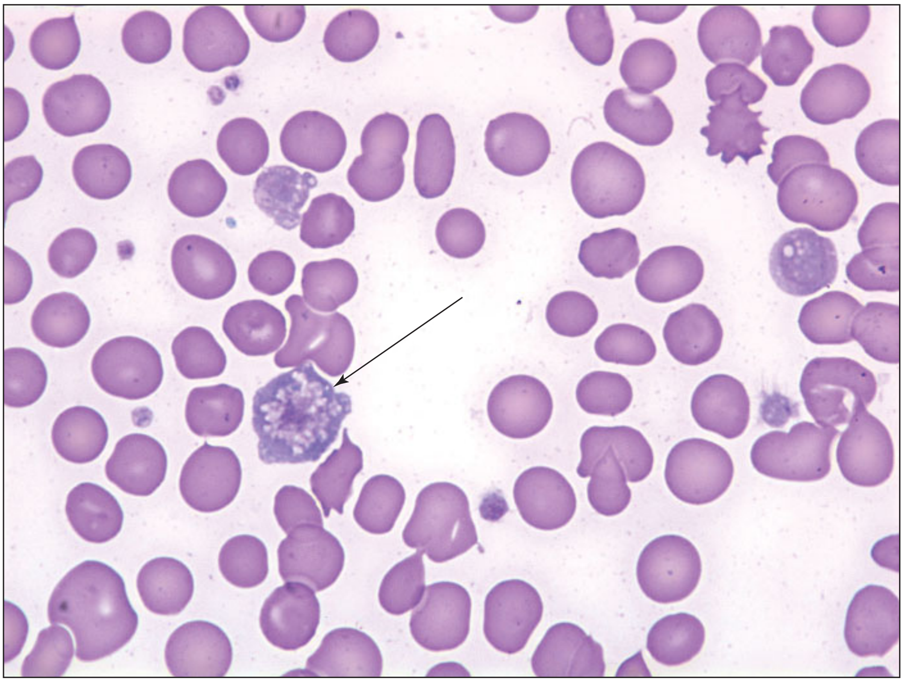


Figure IA3-6

Cell Type

Platelet

Description

Platelet as large as or larger than erythrocytes or granulocytes; light blue with small reddish-blue granules or degranulated (pale blue with no granules)

Clinical Conditions

- May-Hegglin syndrome
- Myeloproliferative diseases
- Splenectomy
- Myelodysplastic syndromes

Large Megakaryocyte

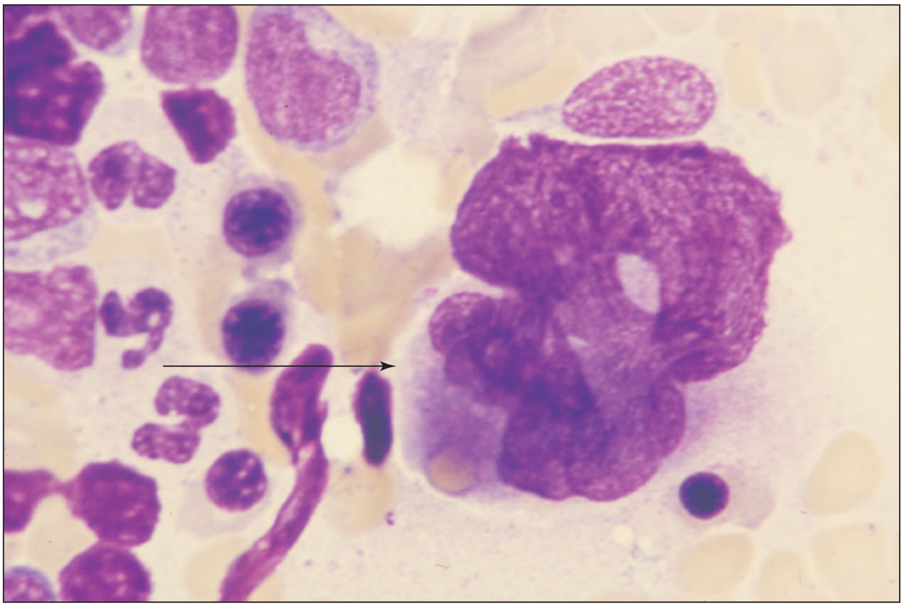


Figure **IA3-7**

Cell Type

Megakaryocyte

Description

Large megakaryocyte with hyperlobulation

Clinical Conditions

- Vitamin B_{12} deficiency
- Folic acid deficiency
- Myelodysplastic syndromes
- Idiopathic thrombocytopenic purpura

Large Mononuclear Megakaryocyte

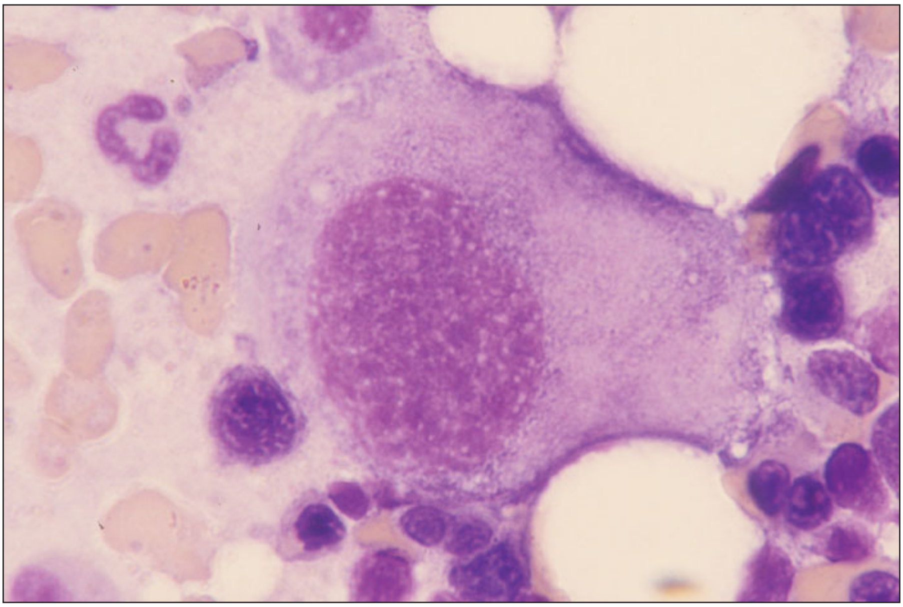


Figure IA3-8

Cell Type

Megakaryocyte

Description

Large megakaryocyte with a single nucleus

Clinical Conditions

- Myelodysplastic syndromes
- Acute megakaryoblastic leukemia (M7) (FAB)
- Acute megakaryoblastic leukemia (WHO)

Micromegakaryocyte

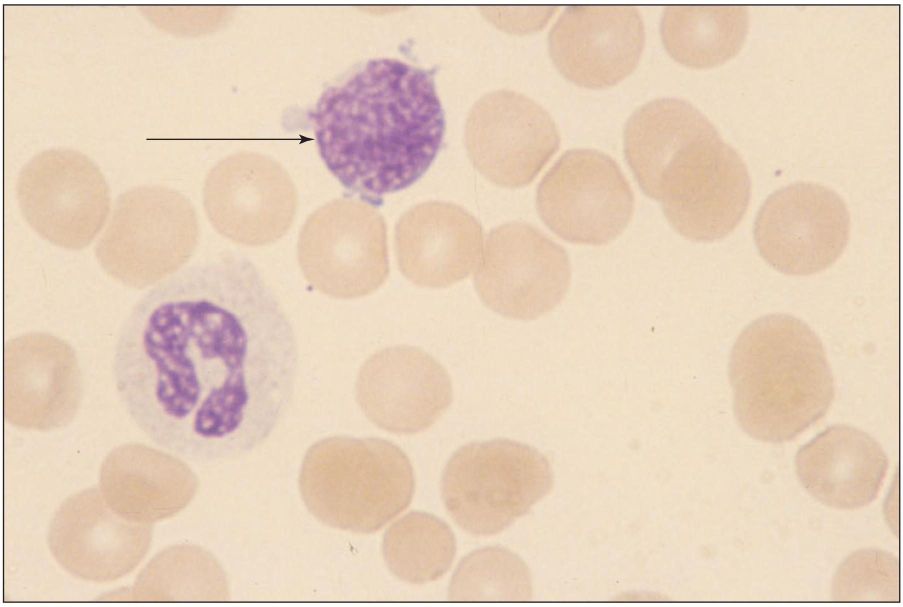


Figure IA3-9

Cell Type

Megakaryocyte

Description

Small megakaryocyte about the size of a lymphocyte
Single-lobed nucleus resembles medium-sized lymphocyte
One or more platelet fragments attached to nucleus or scant cytoplasm

Clinical Conditions

- Myeloproliferative diseases
- Myelodysplastic syndromes
- Acute megakaryoblastic leukemia (M7) (FAB)
- Acute megakaryoblastic leukemia (WHO)

Vacuolated Megakaryocyte

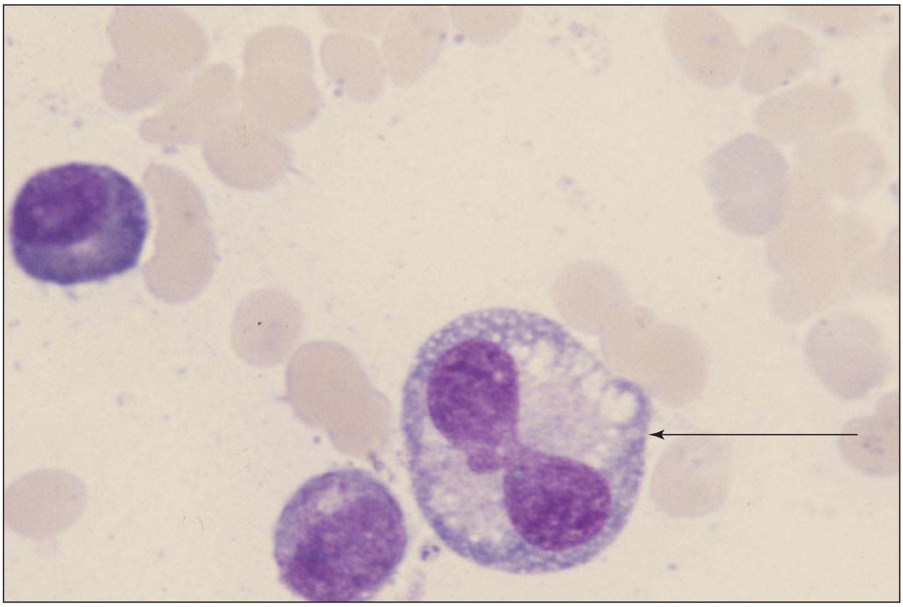


Figure IA3-10

Cell Type

Megakaryocyte

Description

Megakaryocyte or promegakaryocyte with a single or bilobed nucleus
Vacuoles in the basophilic or minimal granule-forming cytoplasm

Clinical Conditions

- Myelodysplastic syndromes
- Acute megakaryoblastic leukemia (M7) (FAB)
- Acute megakaryoblastic leukemia (WHO)

CHAPTER 4

Comparison of Cells

Myeloblast, Myelocyte

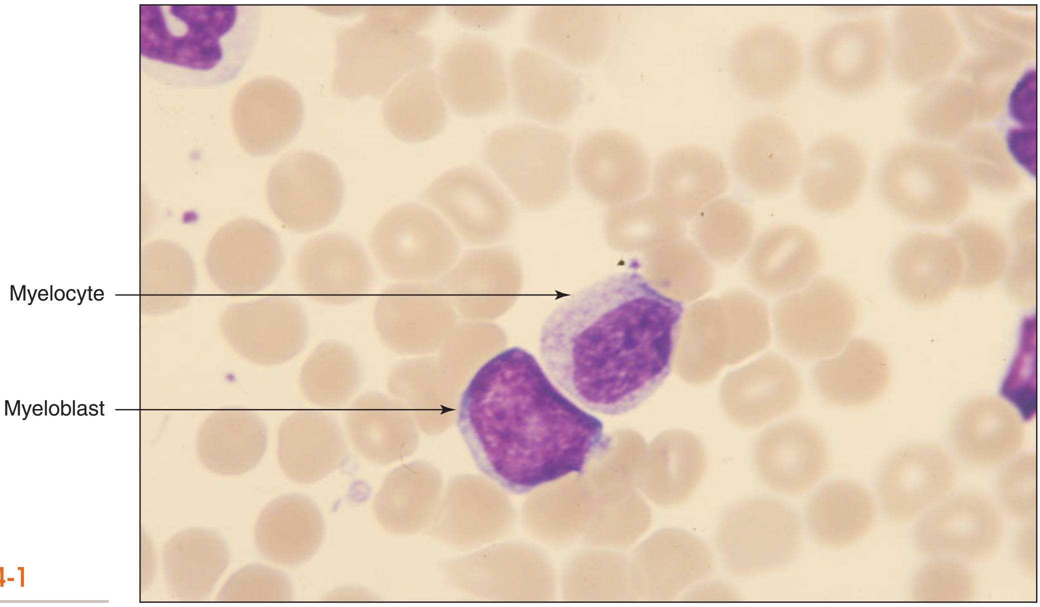


Figure IA4-1

Myeloblast

Fine nuclear chromatin
Moderate amount of agranular blue cytoplasm
N/C ratio higher

Myelocyte

Moderately clumped deep purple nucleus
Presence of some residual primary granules and the beginning of some secondary granule formation in the cytoplasm

Myeloblast, Promyelocyte, Myelocyte

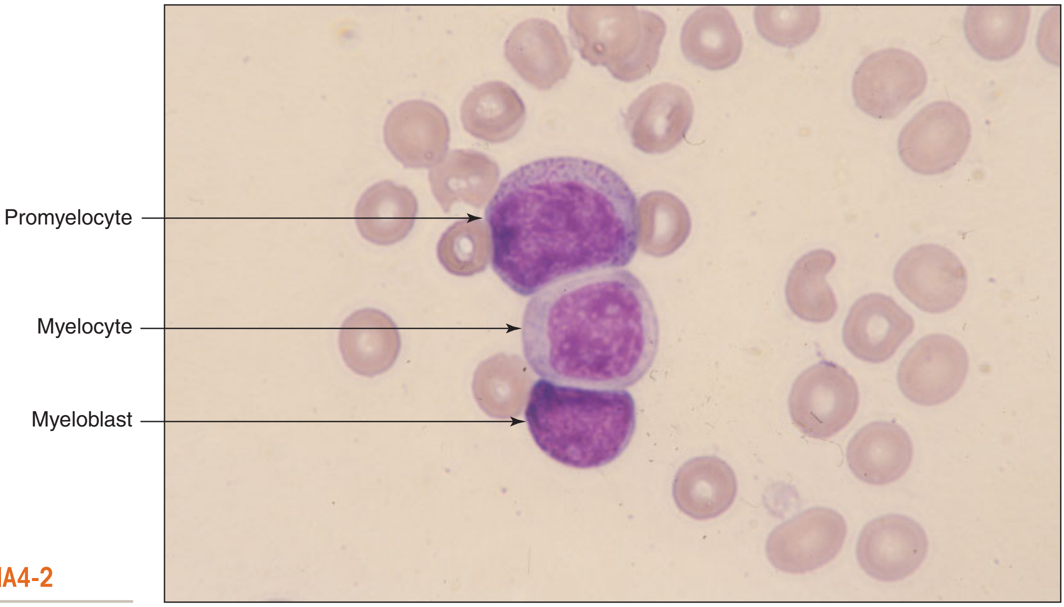


Figure IA4-2

Myeloblast

Highest N/C ratio
Finest nuclear chromatin pattern

Promyelocyte

Presence of primary azurophilic granules
Cytoplasm is moderate blue color

Myelocyte

Lowest N/C ratio
Muddy gray cytoplasmic color
Secondary granules are present
Nuclear chromatin is more clumped

Myeloblast, Basophilic Normoblast

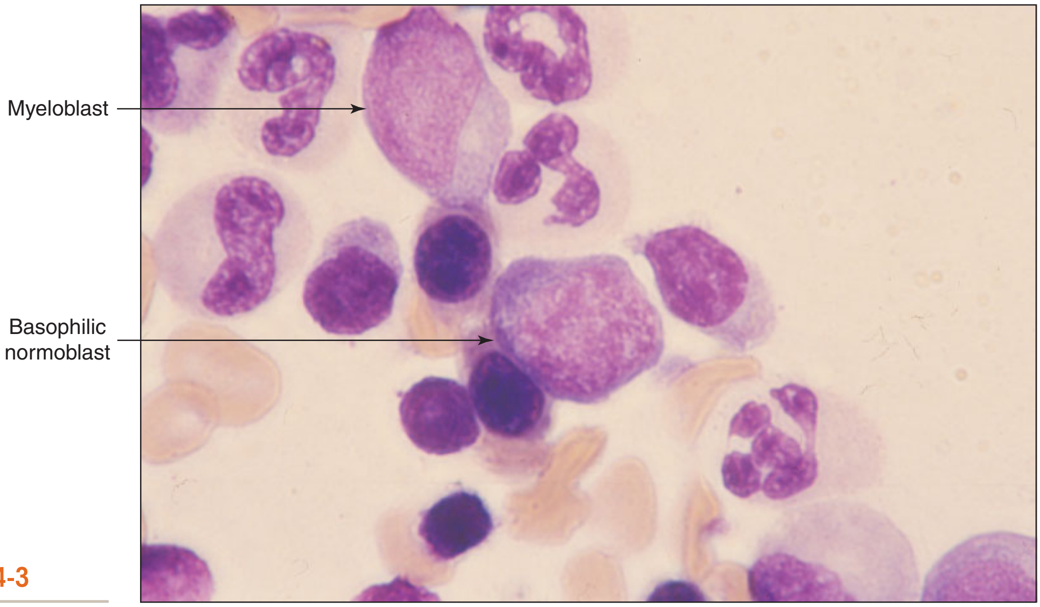

Myeloblast
Basophilic normoblast

Figure **IA4-3**

Myeloblast

Finer nuclear chromatin pattern with visible nucleoli
Cytoplasm has a lighter blue color

Basophilic Normoblast

Nucleus has a more clumped chromatin pattern
Cytoplasm has a deeper blue color

Late Polychromatophilic Normoblast, Lymphocyte

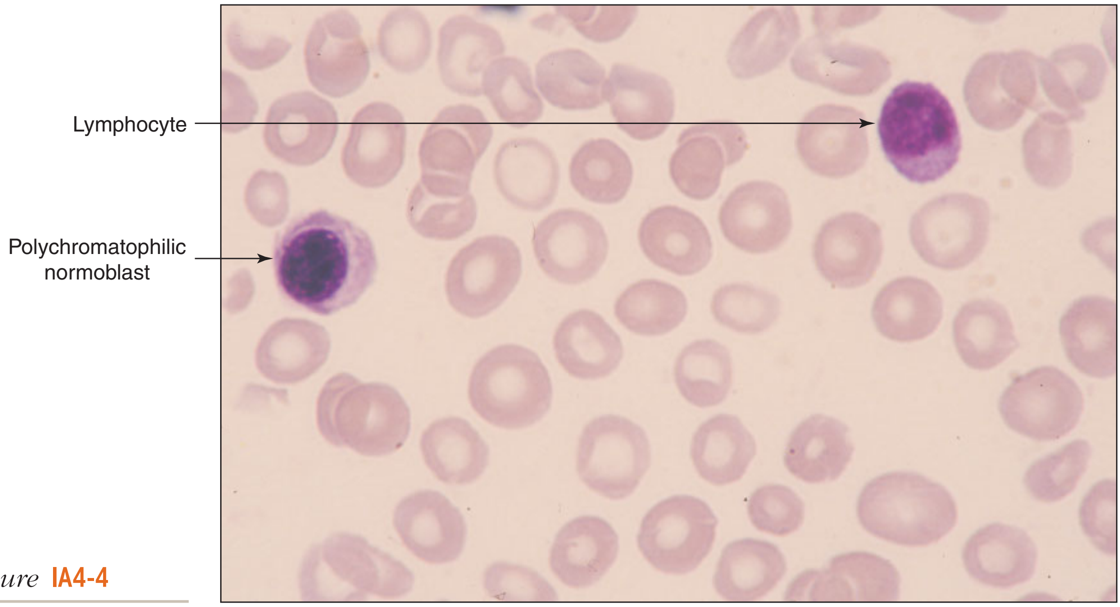

Lymphocyte
Polychromatophilic normoblast

Figure IA4-4

Late Polychromatophilic Normoblast

Nucleus is deep purple and slightly eccentric
Nuclear chromatin is intensely condensed
Cytoplasm is pink with a bluish tinge

Lymphocyte

Nucleus is pale purple and eccentric
Nuclear chromatin is moderately condensed
Cytoplasm is light blue and scanty

Monoblast, Promonocyte

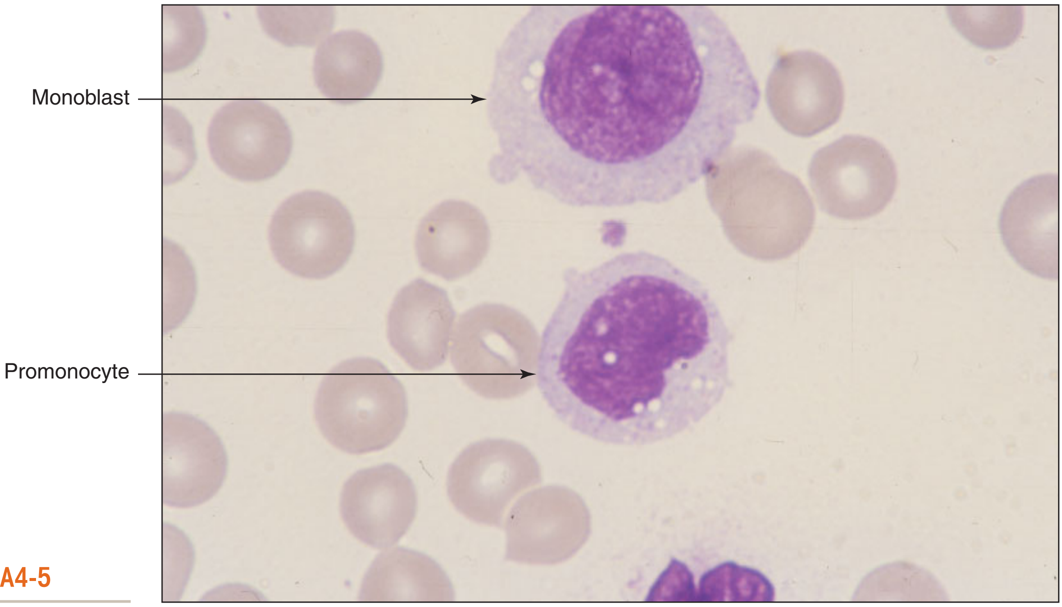


Figure **IA4-5**

Monoblast

Larger cell
Round nucleus with cleave evident
One single nucleoli present
Similar cytoplasms

Promonocyte

Indented nucleus with a more condensed chromatin pattern

Monoblast, Myeloblast

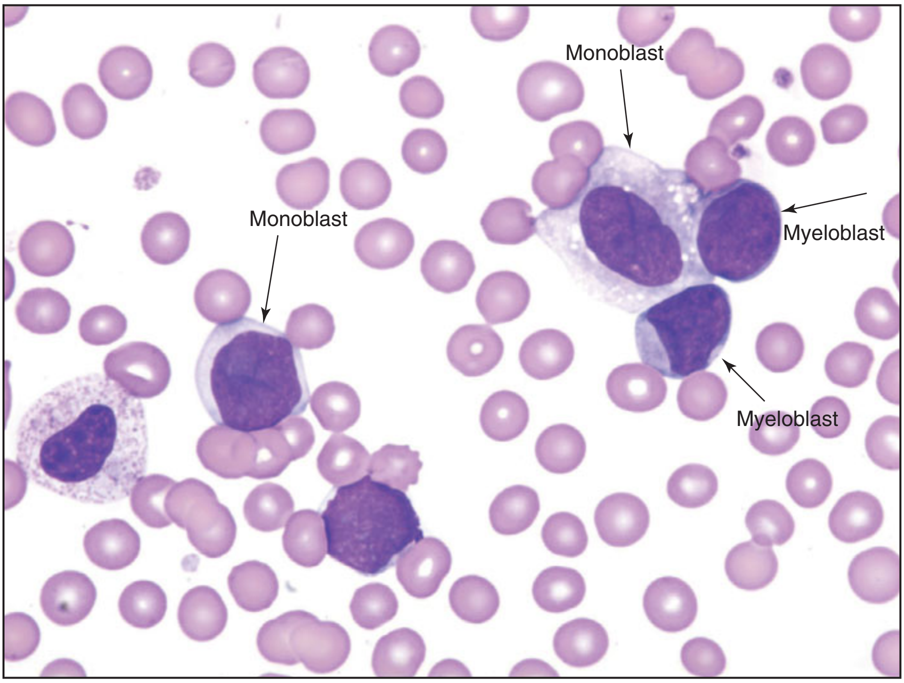

Monoblast
Monoblast
Myeloblast
Myeloblast

Figure **IA4-6**

Monoblast

More cytoplasm
Nucleus has finely dispersed chromatin with a vaguely noticeable cleave

Myeloblast

Higher N/C ratio
Finer chromatin pattern
Smaller cell

Monocyte, Reactive Lymphocyte

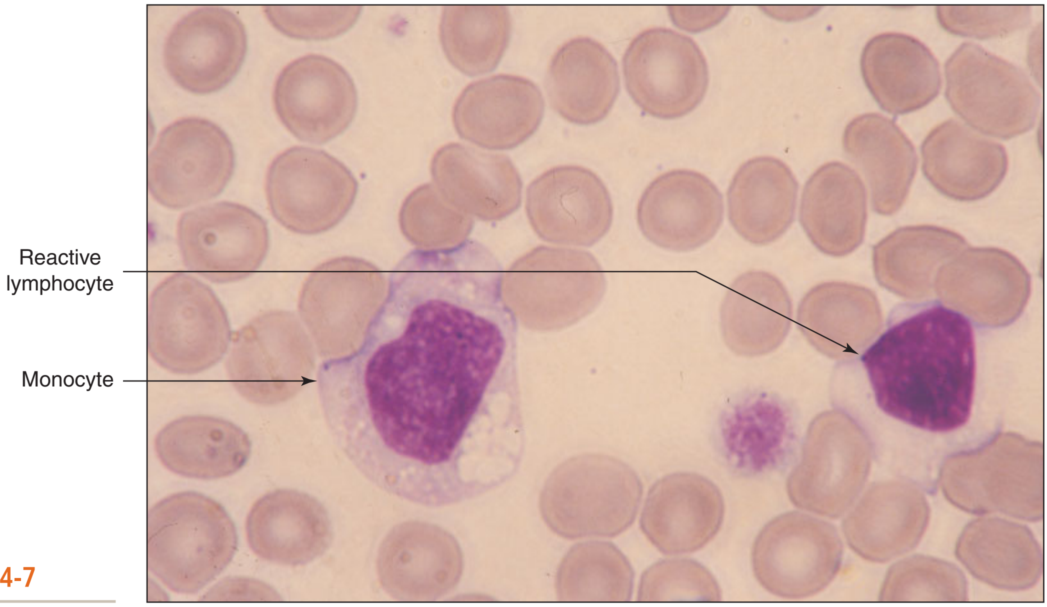

Reactive lymphocyte
Monocyte

Figure **IA4-7**

Monocyte

Cell is larger
Lower N/C ratio
Finer nuclear chromatin pattern

Reactive Lymphocyte

Cell is smaller
Condensed nuclear chromatin pattern
Higher N/C ratio

Monocyte, Lymphocyte

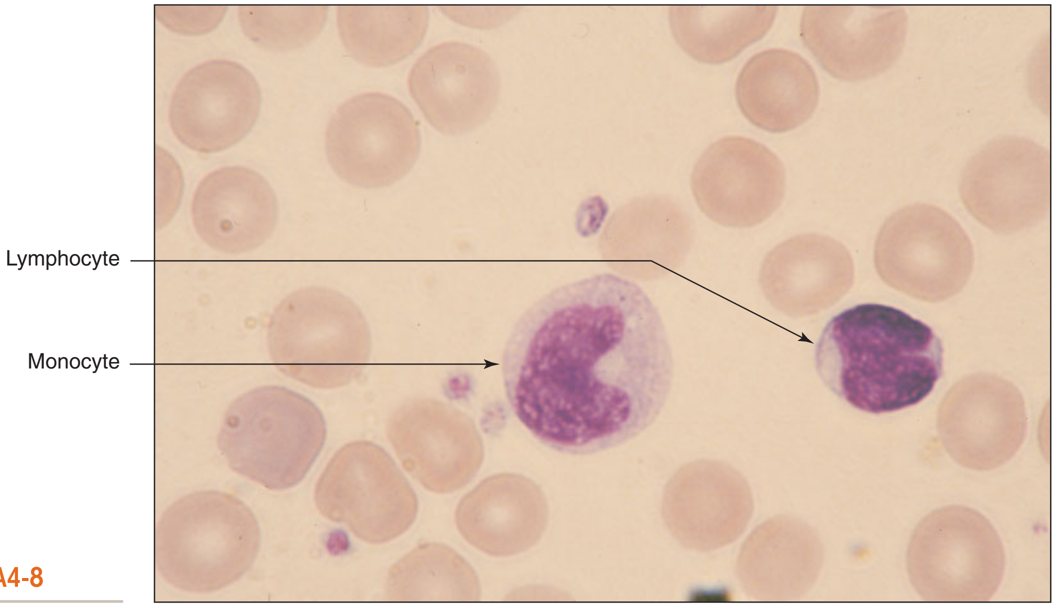


Figure IA4-8

Monocyte

Lower N/C ratio
Finer, lacy nuclear chromatin pattern
Nucleus is indented
Larger cell

Lymphocyte

Nucleus is indented
Intensely clumped nucleus
Higher N/C ratio

Pronormoblast, Myelocyte

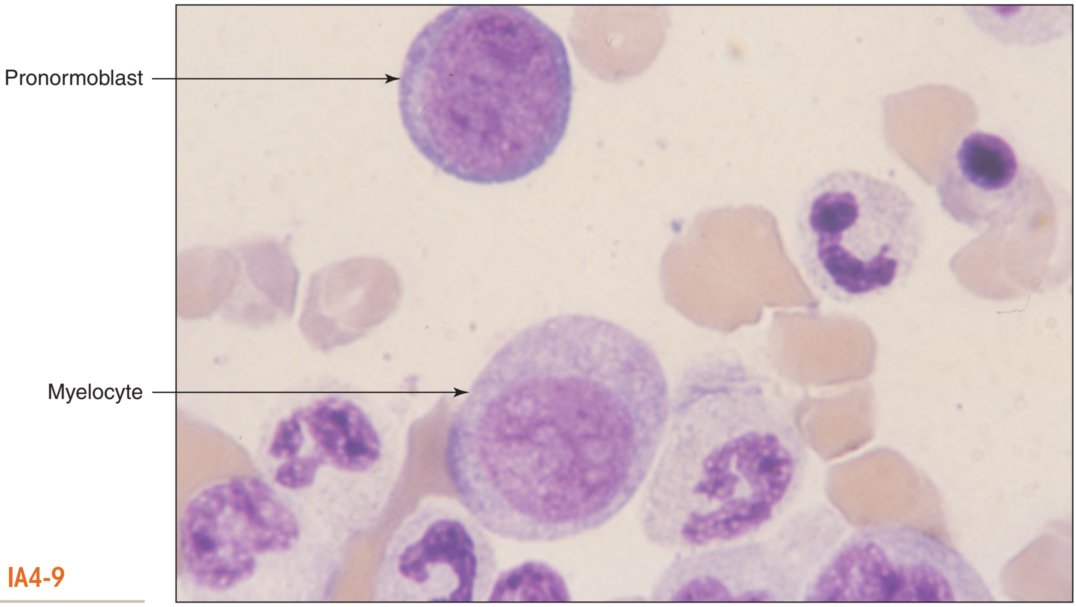


Figure **IA4-9**

Pronormoblast

Nucleus is large, deep purple, and centrally located
Nuclear chromatin is finely stippled
Cytoplasm is intensely basophilic, with light areas of mitochondria
High N/C ratio

Myelocyte

Nucleus is light purple and slightly off center
Nuclear chromatin is moderately condensed, with a prominent nucleoli (nucleoli can still be present since this cell can still divide)
Cytoplasm is grayish-blue with a hint of pink granulation
Lower N/C ratio

Pronormoblast, Promyelocyte

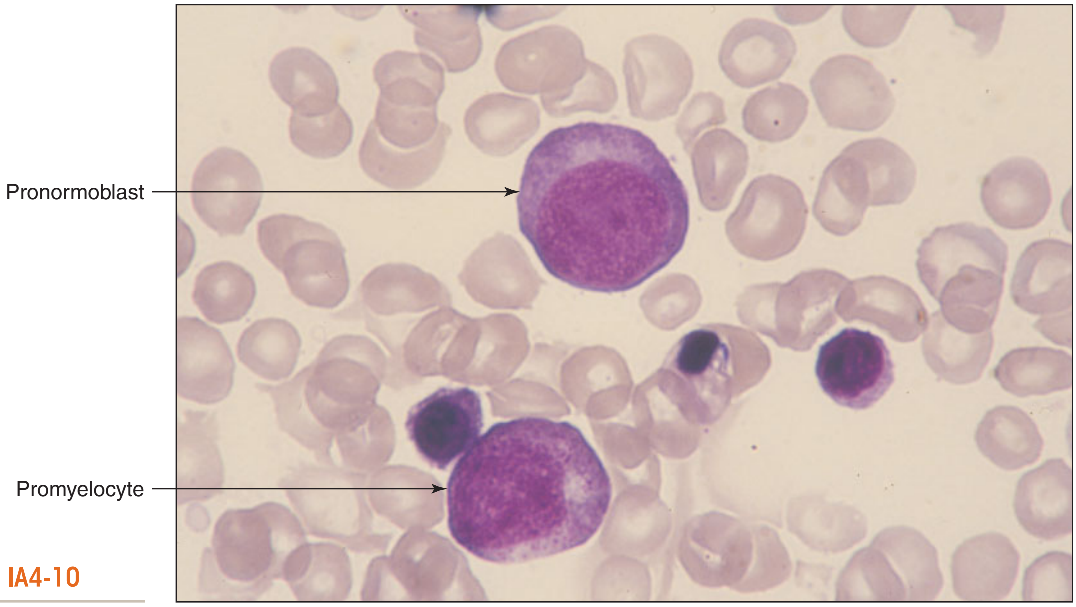


Figure IA4-10

Pronormoblast

Nucleus is large, deep purple, and centrally located
Nuclear chromatin is finely stippled
Cytoplasm is intensely basophilic light areas of mitochondria
Light area next to the nucleus is the Golgi

Promyelocyte

Nucleus is purple and eccentrically located
Nuclear chromatin is finely condensed
Cytoplasm has numerous dark, primary granules that have begun to obscure the nucleus

Early Myelocyte, Late Myelocyte

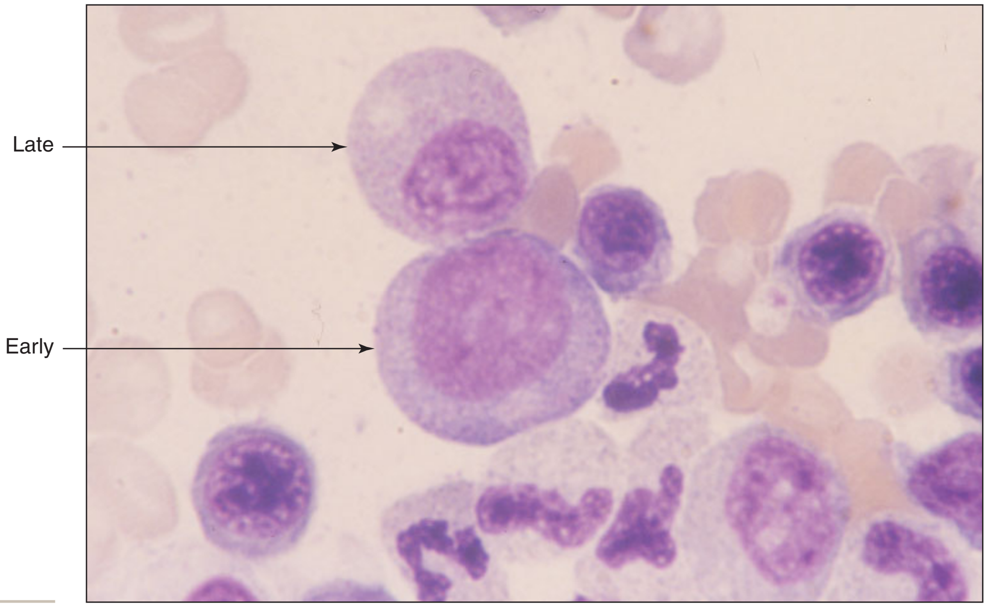


Figure IA4-11

Early Myelocyte

Nucleus is light purple and slightly off center
Nuclear chromatin is moderately condensed, with a prominent nucleoli
Cytoplasm is grayish-blue, with a hint of pink granulation

Late Myelocyte

Nucleus is purple, oval, and eccentric
Nuclear chromatin is fairly clumped and has an aggregated pattern with no visible nucleoli
Cytoplasm is granulated with pink secondary granules

Metamyelocyte, Neutrophilic Band, Neutrophil

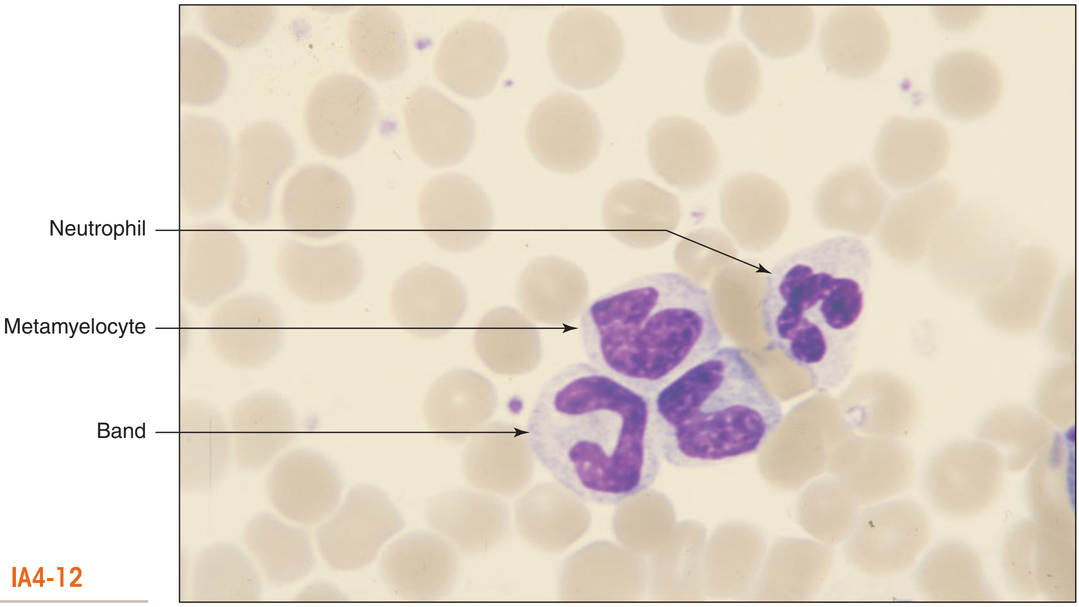


Figure IA4-12

Metamyelocyte

Nucleus is deep purple and has a kidney to slightly indented shape

Nuclear chromatin is fairly coarse but not as clumped as the band or segmented neutrophil

Neutrophilic Band

Nucleus is deep purple and markedly indented to make a band shape

Nuclear chromatin is intensely clumped

Segmented Neutrophil

Nucleus is deep purple and has a segmented shape

Nuclear chromatin is coarsely clumped

Cytoplasm for all three cells is basically the same and seldom helpful in differentiating the cells

Section B
Bone Marrow

CHAPTER 1

Cellularity

NORMAL CELLULARITY

Normal Adult Cellularity

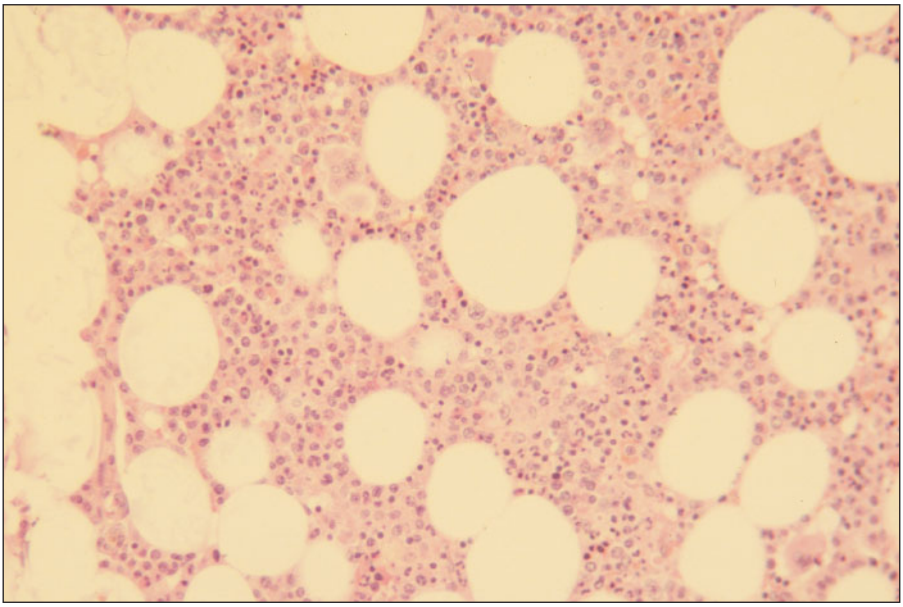


Figure IB1-1

Description

30–80% cellularity

Normal Elderly Cellularity

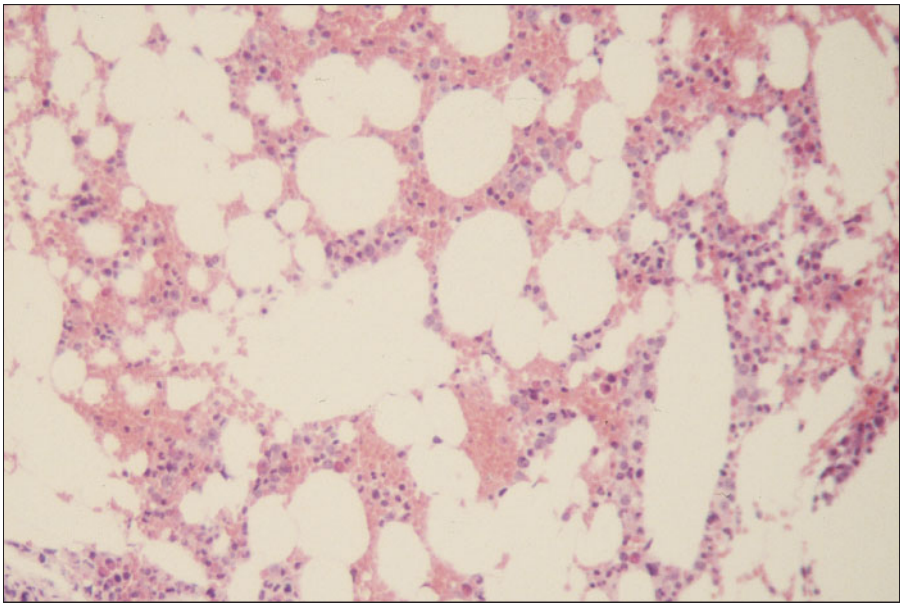


Figure IB1-2

Description

20–50% cellularity

Normal Adolescent Cellularity

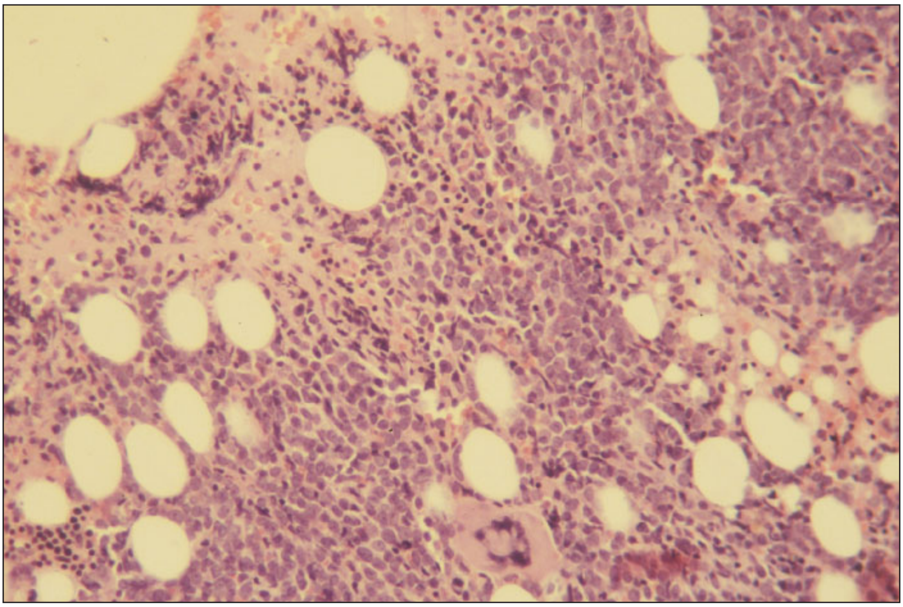


Figure **IB1-3**

Description

50–90% cellularity

Normal Newborn Cellularity

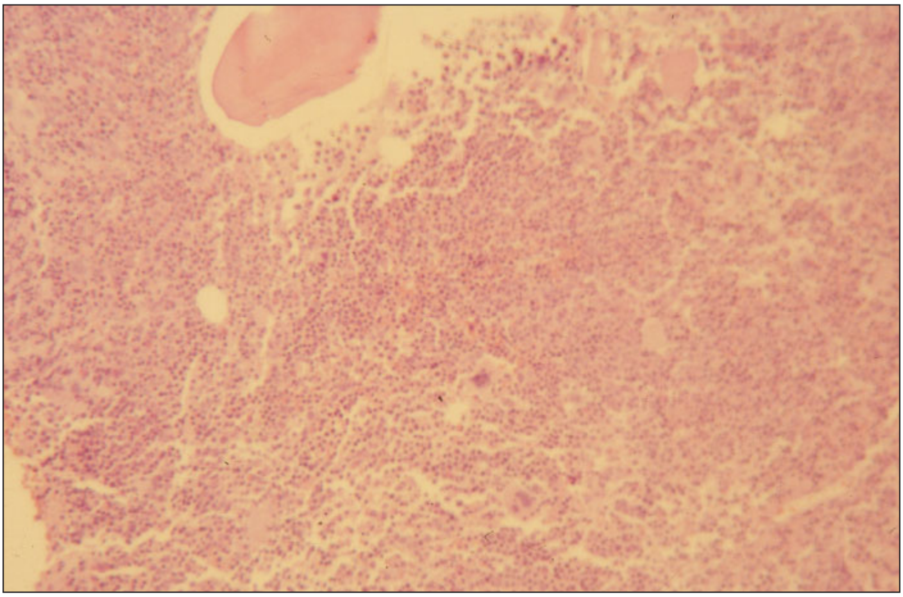


Figure **IB1-4**

Description

75–100% cellularity

Adult Hypocellularity

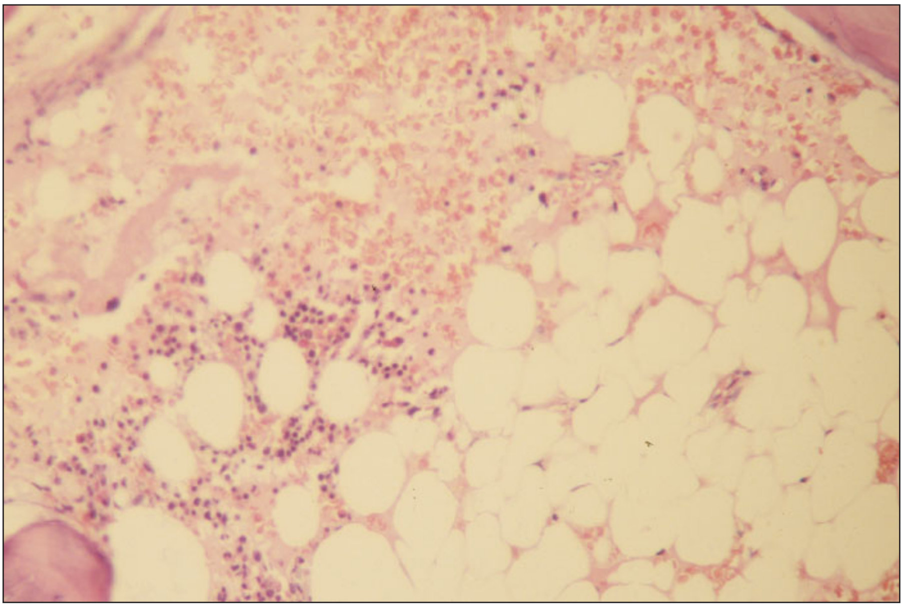


Figure IB1-5

Description

<20% cellularity

Clinical Conditions

- Production disorder
- Aplastic anemia
- Anorexia nervosa

Adult Hypercellularity

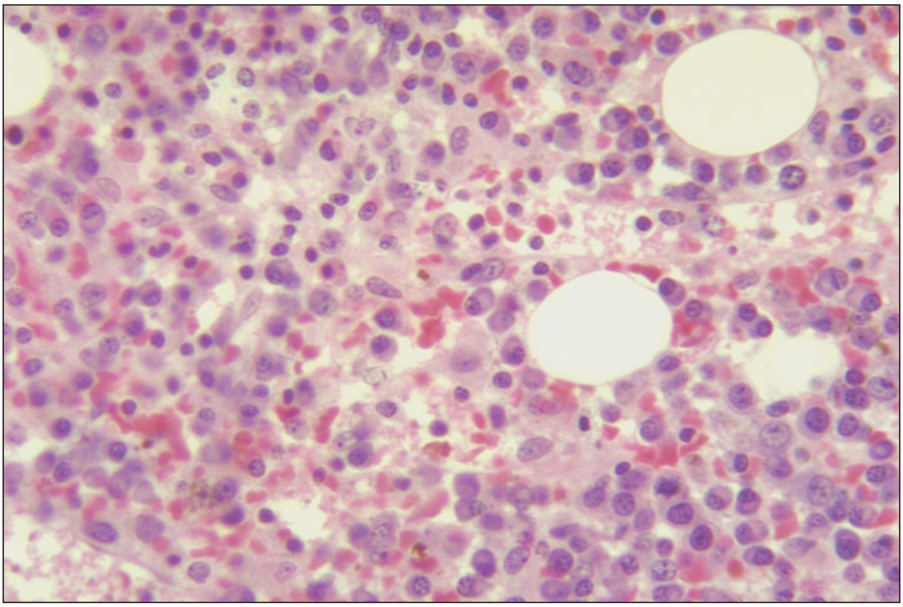


Figure IB1-6

Description

>50% cellularity

Clinical Conditions

- Ineffective hematopoiesis; increased peripheral destruction
- Malignancies
- Reactive processes

Erythropoiesis

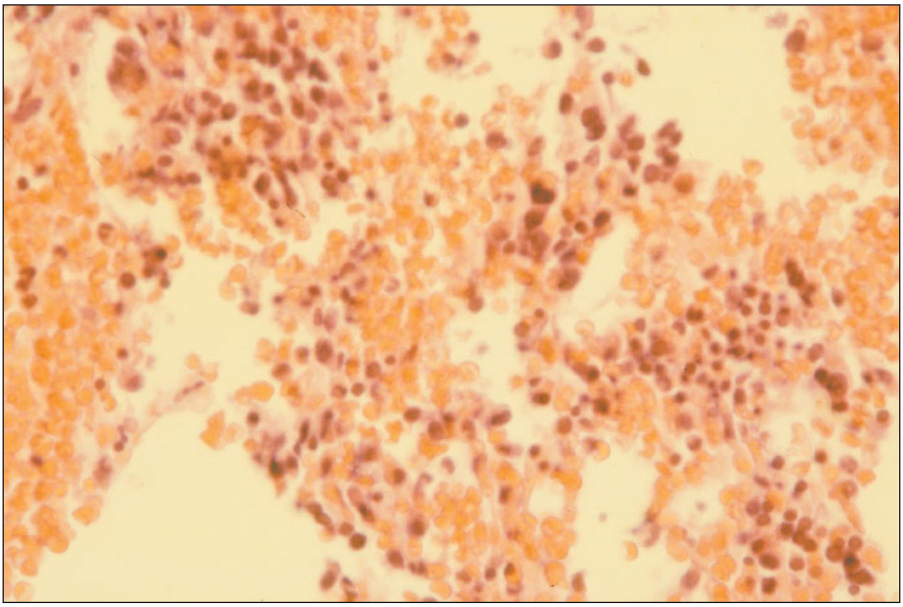


Figure IB1-7

Description

>30% of marrow cellularity is erythrocytic

Clinical Conditions

- Increased M:E ratio—decreased production of erythrocytes
- Decreased M:E ratio—increased production of erythrocytes or ineffective erythropoiesis

Granulopoiesis

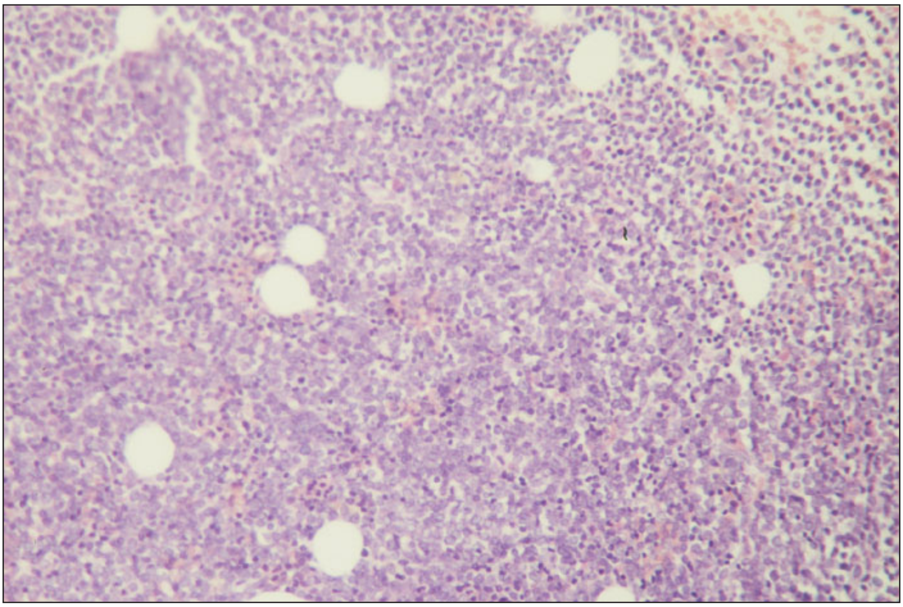


Figure **IB1-8**

Description

>40% of marrow cellularity represents granulopoiesis

Clinical Conditions

- Increased M:E ratio—increased granulocyte production
- Decreased M:E ratio—decreased granulocyte production

Lymphopoiesis

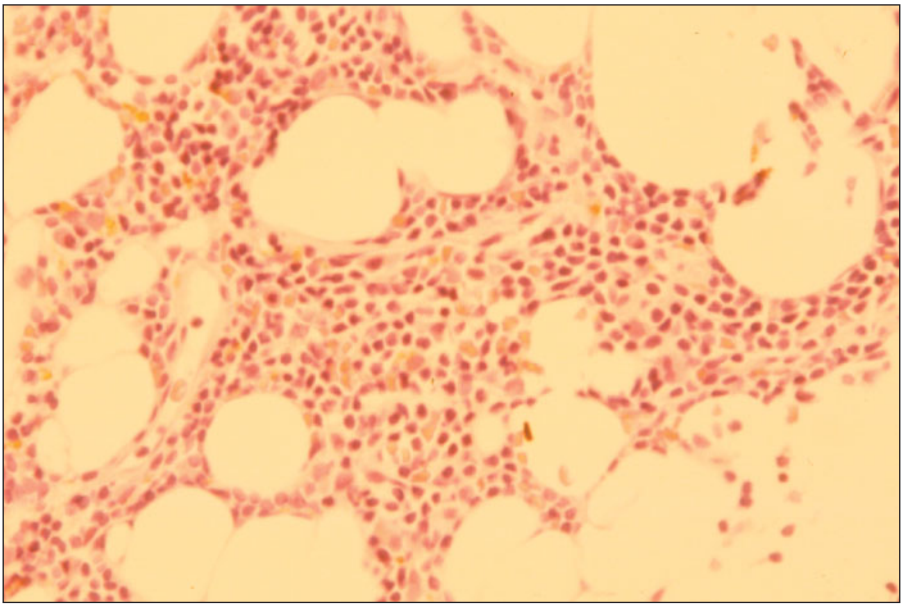


Figure IB1-9

Description

>20% of marrow cellularity is lymphocytic cells

Clinical Conditions

- Lymphoproliferative disorders
- Plasmacytomas
- Marrow aplasias
- Chronic lymphocytic leukemia

Megakaryopoiesis

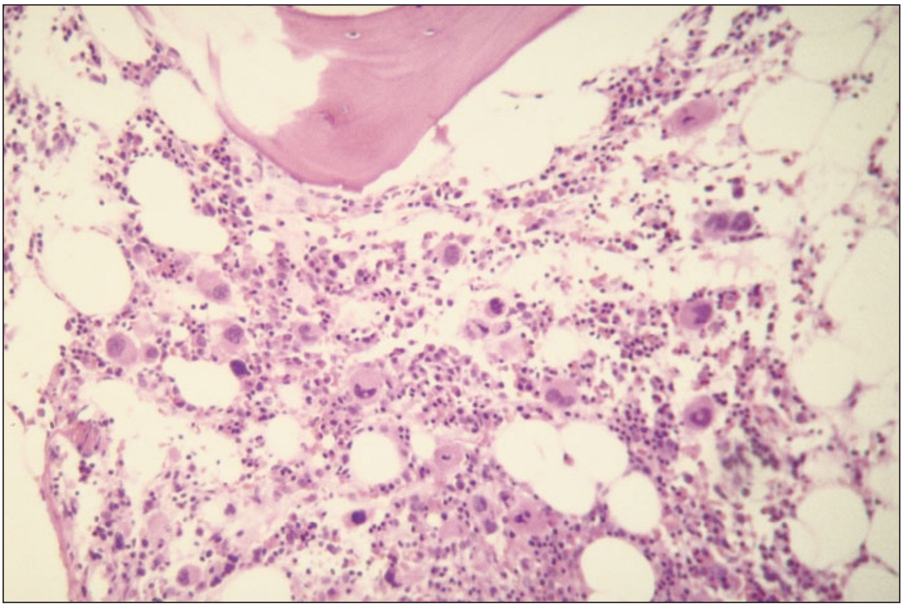


Figure IB1-10

Description

Usually see 1–5 megakaryocytes per 1000 cells

Clinical Conditions

- Idiopathic thrombocytopenic purpura
- Myeloproliferative syndromes
- Some myelodysplastic syndromes—5 q-syndrome
- Acute megakaryoblastic leukemia (M7) (FAB)

CHAPTER 2

Cells of the Reticuloendothelial System

♦ NORMAL CELLS

Macrophage

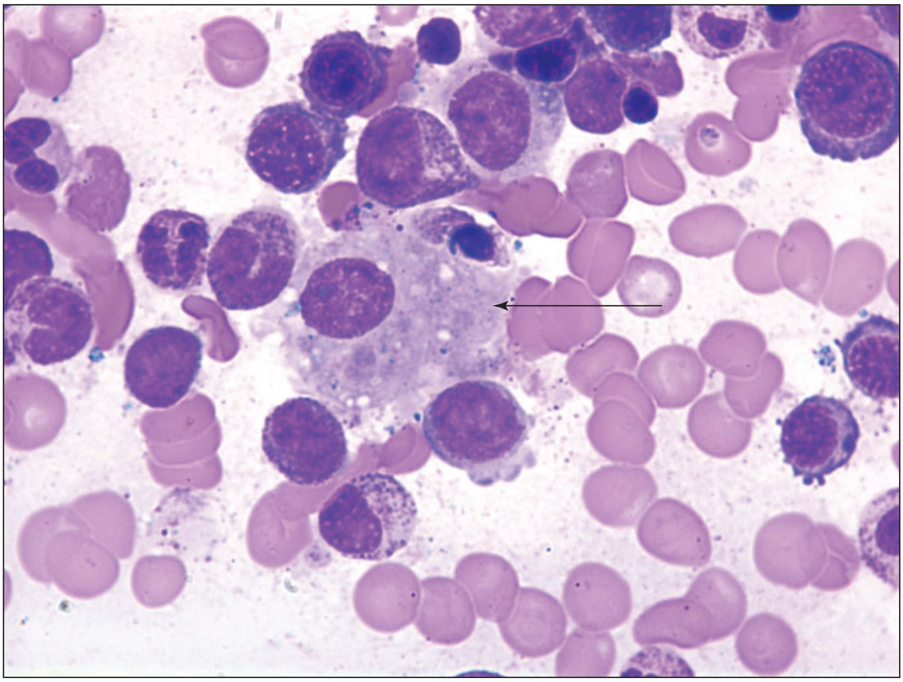


Figure IB2-1

Size: 15–80 μ

Nucleus

Shape: Egg-shaped, indented, elongated
N/C Ratio: 2:1–1:1
Color: Purple
Chromatin: Spongy
Nucleoli: None

Cytoplasm

Color: Sky blue
Contents: Coarse, azure granules; vacuoles; many neutral red bodies scattered throughout

Reticulum Cell

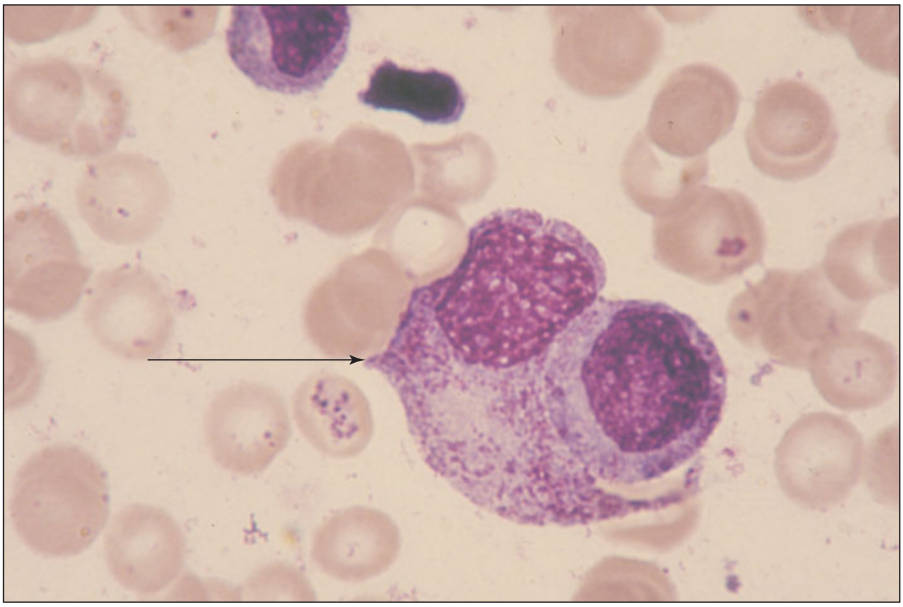


Figure IB2-2

Size: 20–30 μ

Nucleus

Shape: Round to oval
N/C Ratio: 1:1
Color: Purple with reddish hue
Chromatin: Fine, loosely bound but with areas of parachromatin
Nucleoli: 1 or more

Cytoplasm

Irregular outline
Color: Pale, blue, often retracted or folded, caused by smearing technique
Contents: Reticulin fibers that cause an azurophilic appearance; may contain phagocytized materials

ABNORMAL CELLS

Gaucher Cell

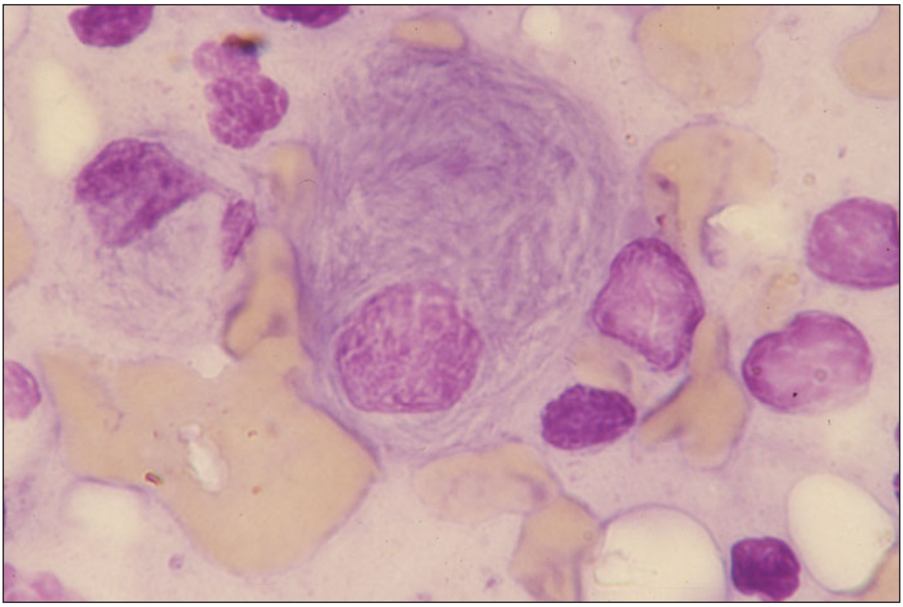


Figure IB2-3

Cell Type

Macrophage

Size: 20–80 μ

Description

A pale-staining cell; the cytoplasm is filled with a fibrillar lipid, which gives the appearance of crumpled tissue paper or a wrinkled look; the nucleus is small, round, and eccentrically placed

Clinical Conditions

- Gaucher disease
- Thalassemia (pseudo–Gaucher cells)
- Chronic myelocytic leukemia (pseudo–Gaucher cells)

Niemann-Pick Cell

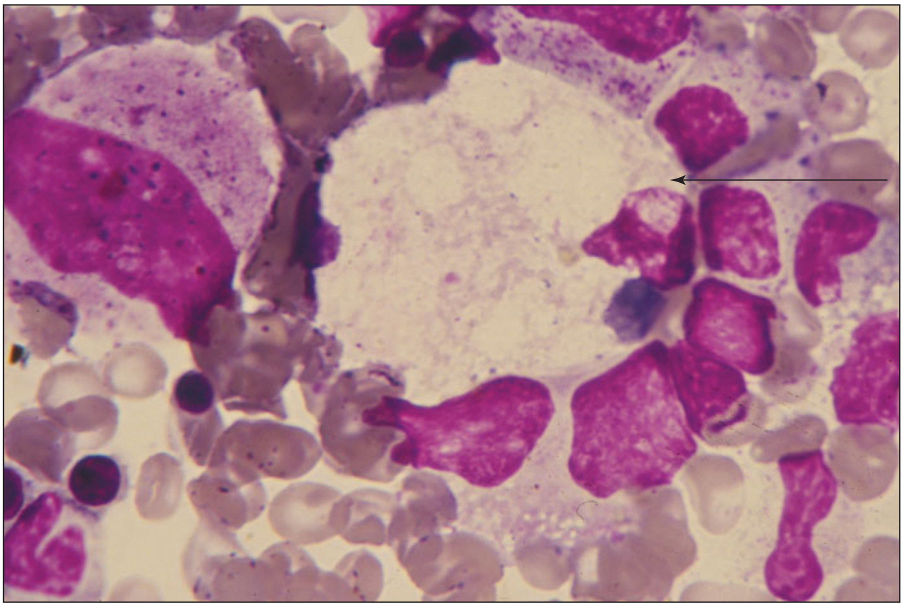


Figure IB2-4

Cell Type

Macrophage

Size: 20–90 μ

Cell Description

Pale staining; cytoplasm contains droplets of sphingomyelin, giving it a globular appearance; the nucleus is small, round, and eccentrically placed

Clinical Condition

- Niemann-Pick disease

Sea-Blue Histiocyte

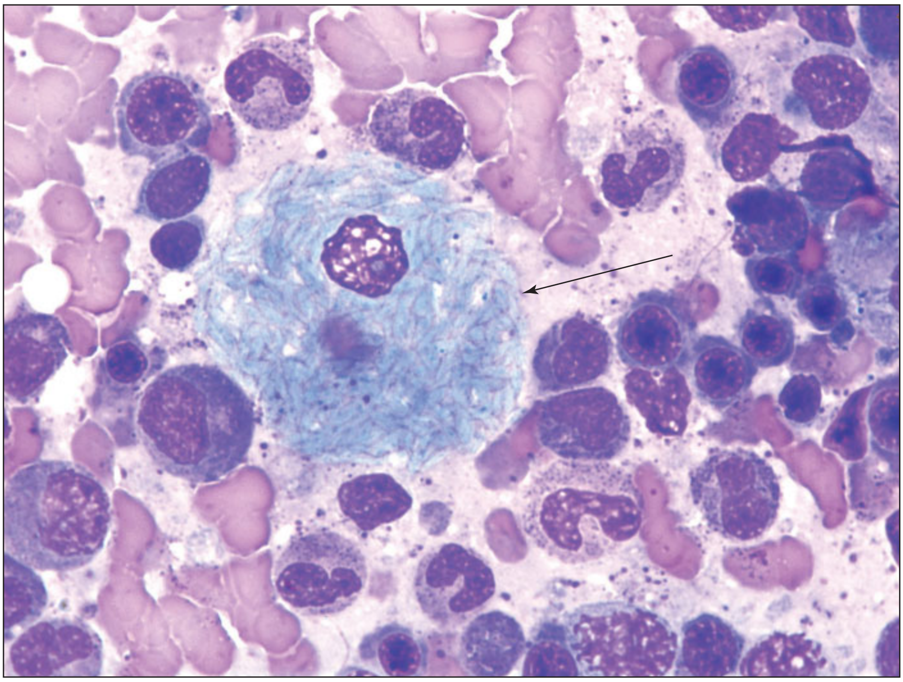


Figure **IB2-5**

Cell Type

Histiocyte

Size: 20–60 µ

Description

Cell containing granules that stain a sea-blue or blue-green; nucleus is small, round, and eccentric, with block chromatin

Clinical Conditions

- Sea-blue histiocytosis
- Pseudo–sea-blue histiocytes are seen in the following:
  - Thalassemia
  - Chronic myelocytic leukemia
  - Polycythemia vera
  - Sickle cell anemia
  - Sarcoidosis
  - Chronic granulomatous disease

CHAPTER 3

Nonhematopoietic Cells

Osteoblast

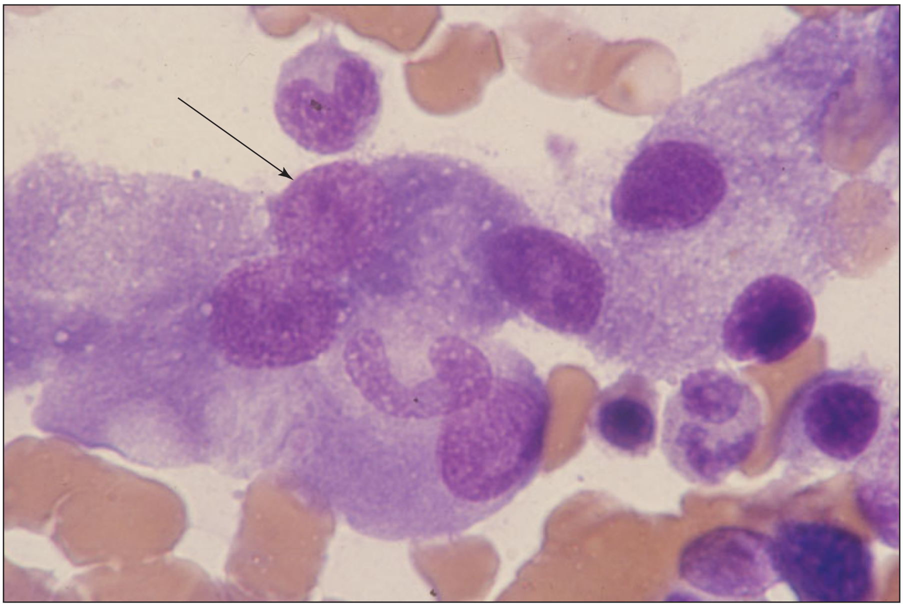


Figure IB3-1

Size: Frequently Found in Clumps, but Each Individual Cell Ranges from 25–50 μ

Nucleus

Shape: Oval or round; eccentric
N/C Ratio: 1:3–1:4
Color: Purple
Chromatin: Finely granular with clumps; some areas of parachromatin
Nucleoli: 1–3 present, small, light blue

Cytoplasm

Color: Pale blue to dark blue with blurred outlines
Contents: Round, pink-gray areas (archoplasm)

Osteoclast

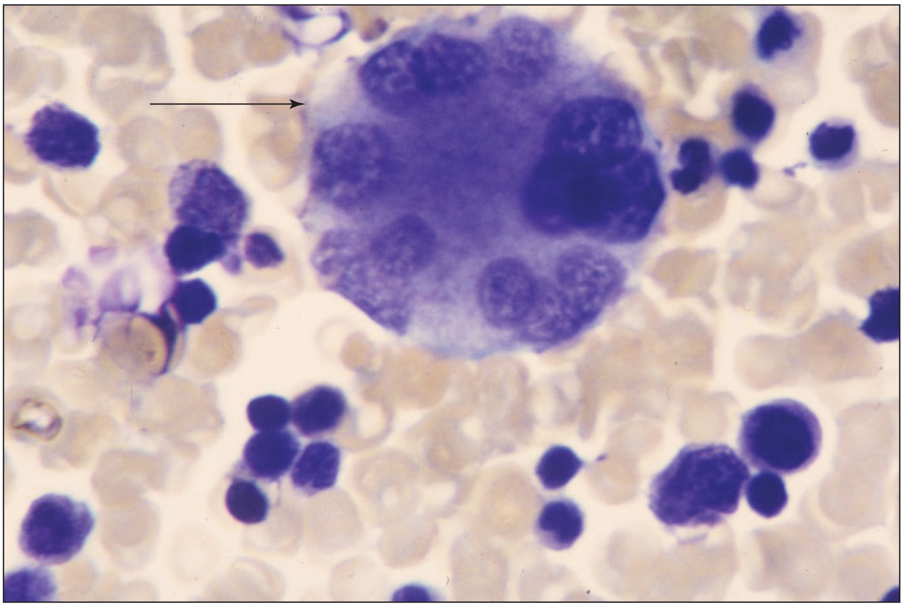


Figure IB3-2

Size: Usually >100 μ

Nucleus

Polyploid and scattered throughout cell; not interconnected
Shape: Round
N/C Ratio: 4:1–2:1–1:1
Color: Purple
Chromatin: Dense
Nucleoli: Usually 1–2 present in each nucleus

Cytoplasm

Color: Light blue to pink, giving a cloudy appearance
Contents: Coarse granules

Section C

Cytochemistry

CHAPTER 1

Cytochemical Stains

ACID PHOSPHATASE REACTION

With Tartrate Inhibition (TRAP)

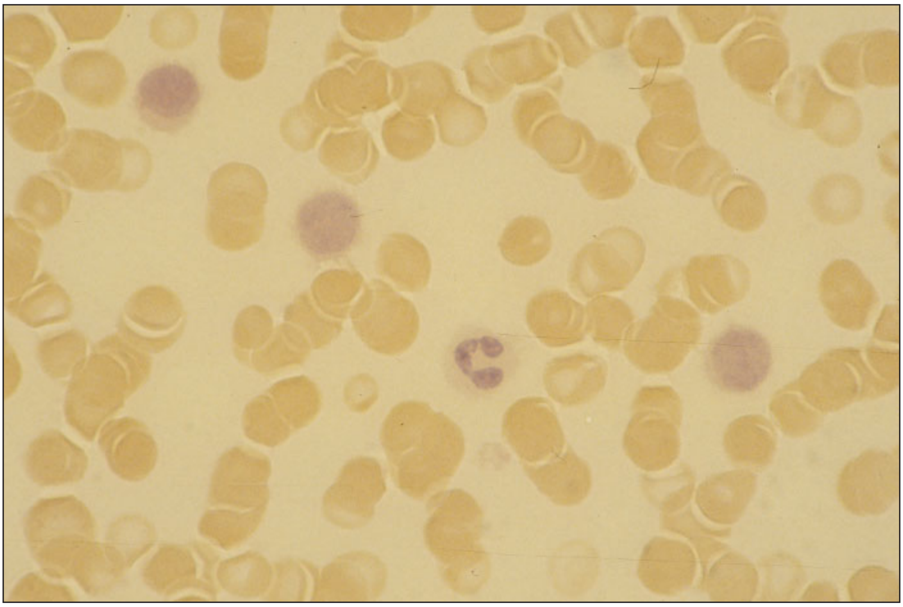


Figure IC1-1

Negative

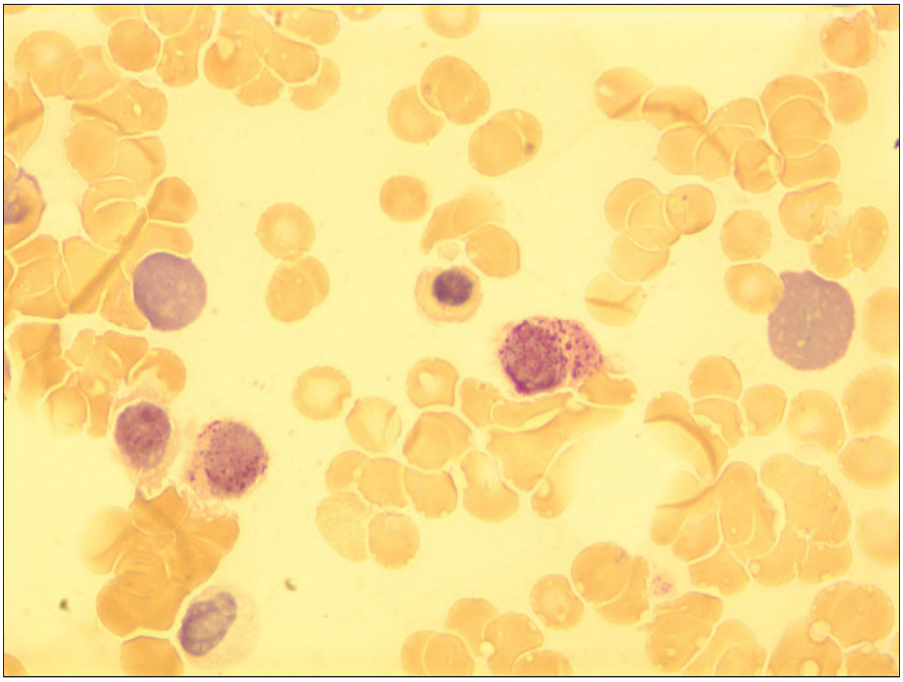


Figure IC1-2

Positive

Cell Type

Hairy cells, histiocytes, activated lymphocytes, and activated macrophages

Description

Acid phosphatase (isoenzyme 5) is resistant to tartrate

Hairy cells and histiocytes contain this acid phosphatase, are resistant to inhibition, and will demonstrate positivity (color is dependent on couplers used)

Clinical Condition

- Hairy cell leukemia

ACID PHOSPHATASE REACTION

Without Tartrate Inhibition

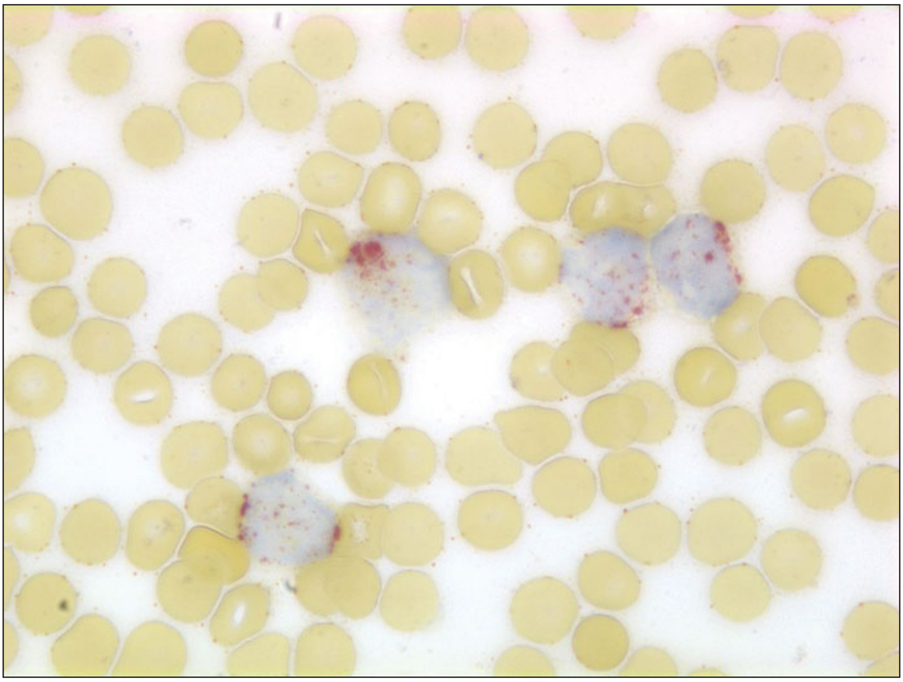


Figure IC1-3

Positive

Cell Type

Most nucleated cells of the hematopoietic system and platelets

Description

Positivity is indicated by a diffuse granular red reaction product

The red product will disappear or contain only a small amount of reactivity after tartrate is added to the reaction

Focal positivity may be found in blasts of T-cell ALL

Clinical Conditions

- Some T-cell precursor lymphoblastic leukemia
- T-cell prolymphocytic leukemia
- T-cell lymphoproliferative disorder
- Sézary syndrome

NONSPECIFIC ESTERASE REACTION

With Fluoride Inhibition

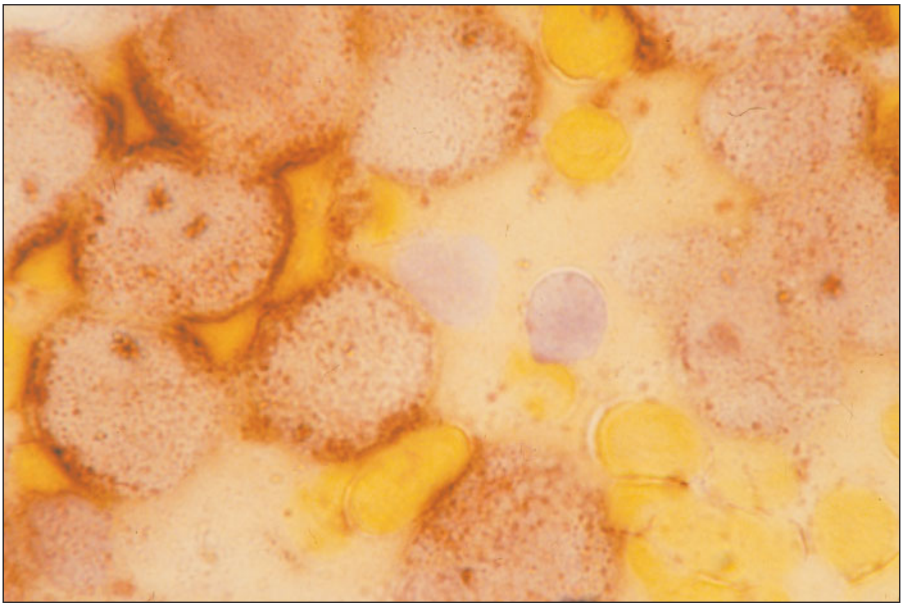


Figure IC1-4

Negative for inhibition.

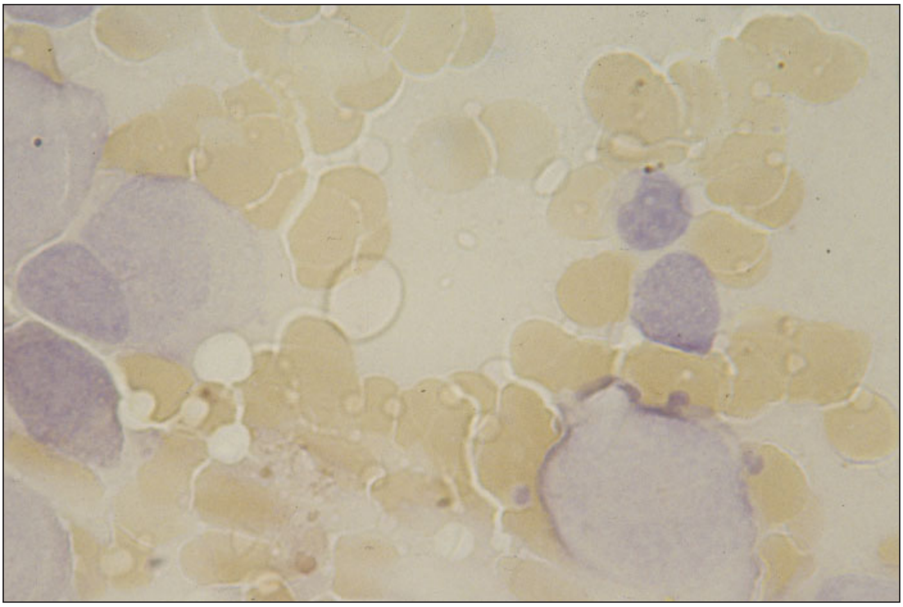


Figure IC1-5

Positive for inhibition.

Cell Type

Monocytic line

Description

Megakaryocytes, histiocytes, and macrophages demonstrate positivity
Lymphocytes may have a punctate positivity or foci of positivity for T-cells
Monocytes are sensitive to fluoride inhibition and will not show positivity

Clinical Conditions

- Acute myelomonocytic (M4) (FAB) and monocytic (M5) (FAB) leukemias are inhibited by fluoride
- Acute lymphocytic leukemia or leukemias of granulocytic origins are not inhibited

NONSPECIFIC ESTERASE REACTION

Without Fluoride Inhibition

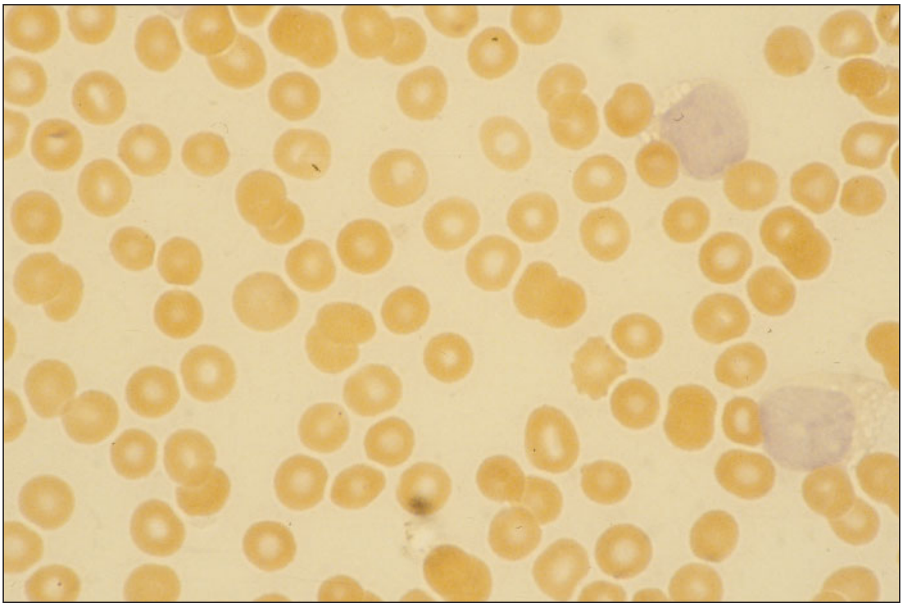


Figure IC1-6

Negative

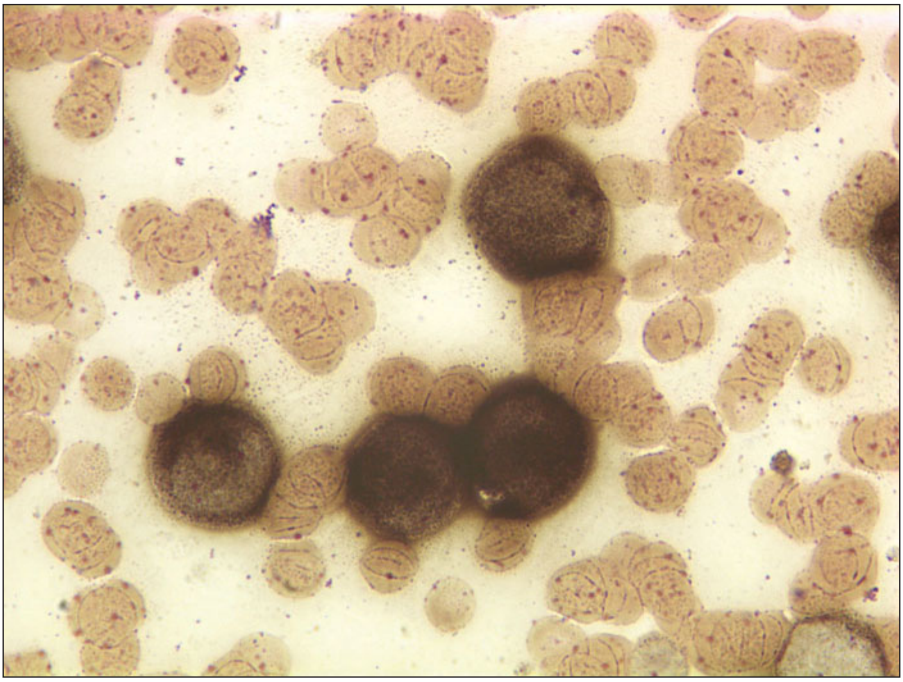


Figure IC1-7

Positive

Cell Type

Monocytic line

Description

Megakaryocytes, histiocytes, and macrophages demonstrate positivity
Lymphocytes may have a punctate positivity or foci of positivity for T-cells
Monocytes are sensitive to fluoride inhibition and will not show positivity

Clinical Conditions

- Acute myelomonocytic (M4) (FAB) and monocytic (M5) (FAB) leukemias are inhibited by fluoride
- Acute lymphocytic leukemia or leukemias of granulocytic origins are not inhibited

SPECIFIC ESTERASE REACTION

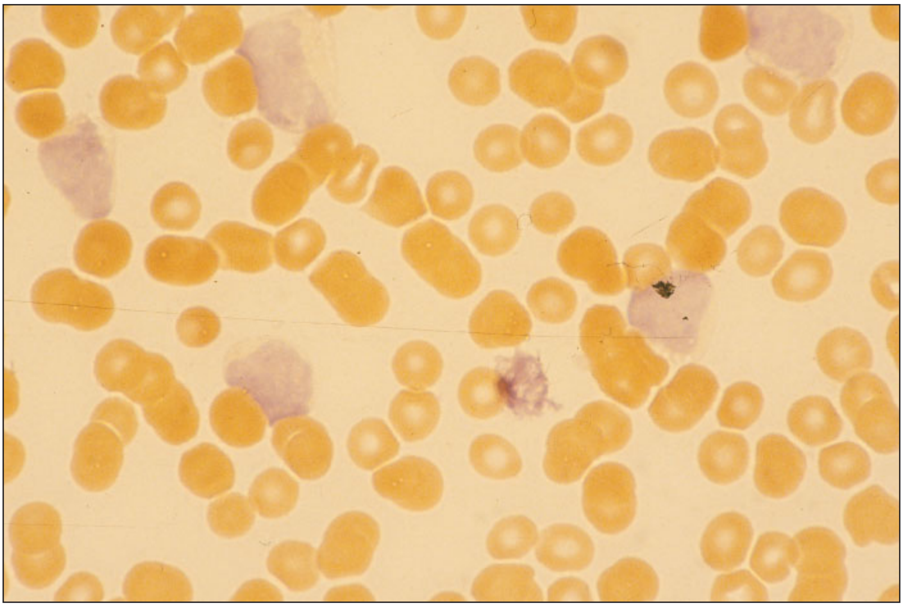


Figure IC1-8

Negative

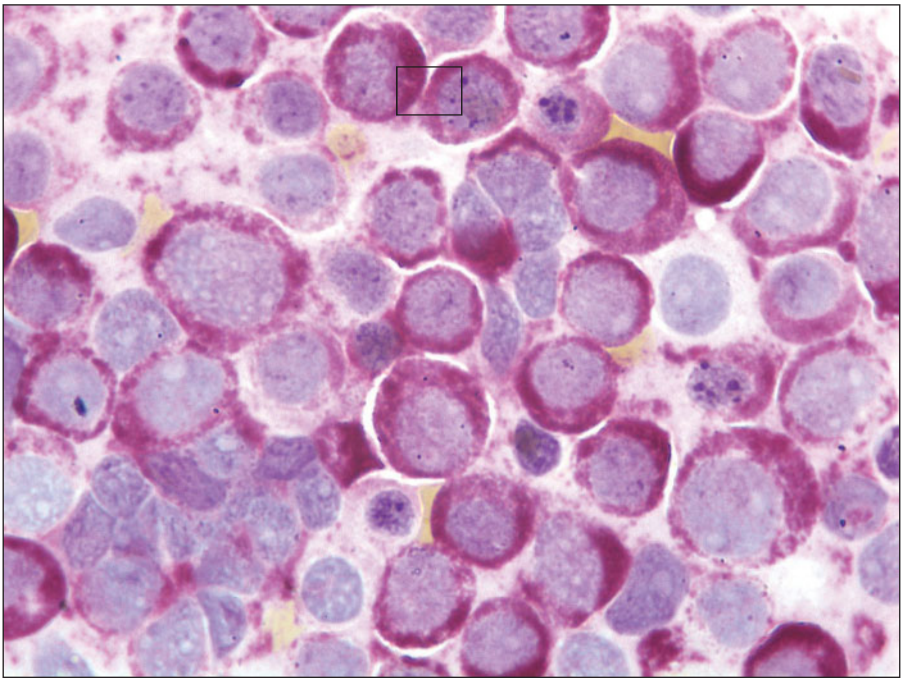


Figure IC1-9

Positive

Cell Type

Some myeloblasts, promyelocytes, myelocytes, metamyelocytes, bands, segmented neutrophils, and abnormal eosinophils

Description

Esterases are enzymes that are capable of hydrolyzing the aliphatic and aromatic ester bonds of the substrate naphthol AS-D chloroacetate

Produces a positive reaction, indicated by red to magenta color

Clinical Conditions

- Differentiates granulocytes from lymphocytes and monocytes
- Acute myelocytic leukemia without maturation (M1) (FAB)
- Acute myelocytic leukemia with maturation (M2) (FAB)
- Acute promyelocytic leukemia (M3) (FAB)
- Acute myelomonocytic leukemia (M4) (FAB)
- Acute myelomonocytic leukemia with abnormal bone marrow eosinophils
- AML with recurrent genetic abnormalities (WHO)
  AML with t(8;21)
  AML with t(15;17)
  AML with inv 16 or t(16;16)

COMBINED ESTERASE REACTION

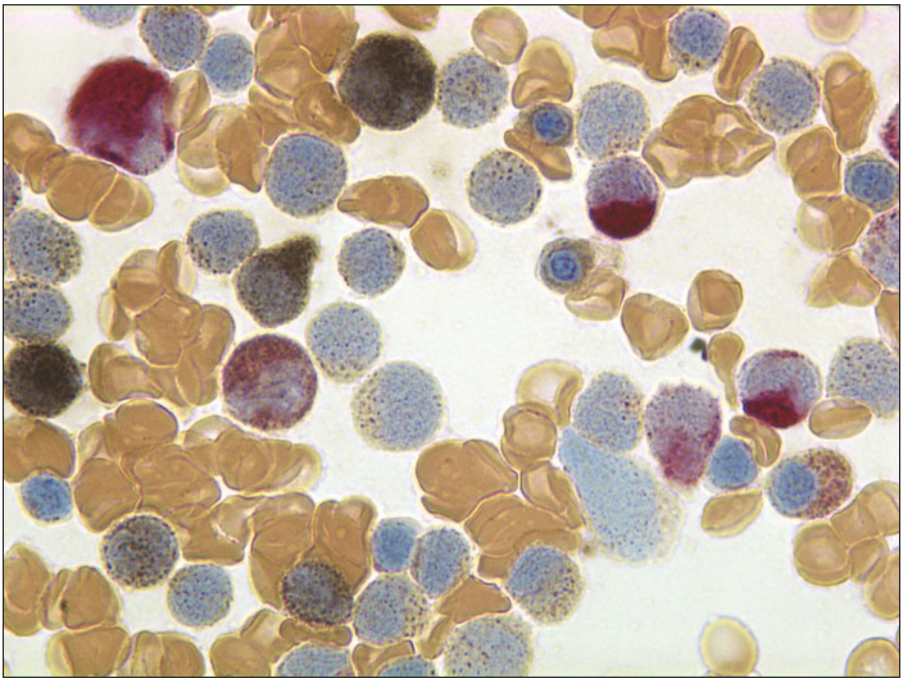


Figure IC1-10

Positive

Cell Type

Differentiation of granulocytic and monocytic series

Description

Both alpha-naphthyl acetate (nonspecific) and naphthyl chloroacetate (specific) are used as substrates

Monocytic series demonstrates positivity with the nonspecific esterase

Granulocytic series demonstrates a positive reaction with the specific esterase (color depends on couplers used)

Clinical Conditions

- Acute myelomonocytic leukemia (M4) (FAB)—demonstrates the coexpression of granulocytic and monocytic enzymes
- Acute monoblastic leukemia (M5a) (FAB)
- Acute monocytic leukemia (M5b) (FAB)

IRON STAIN—PRUSSIAN BLUE REACTION

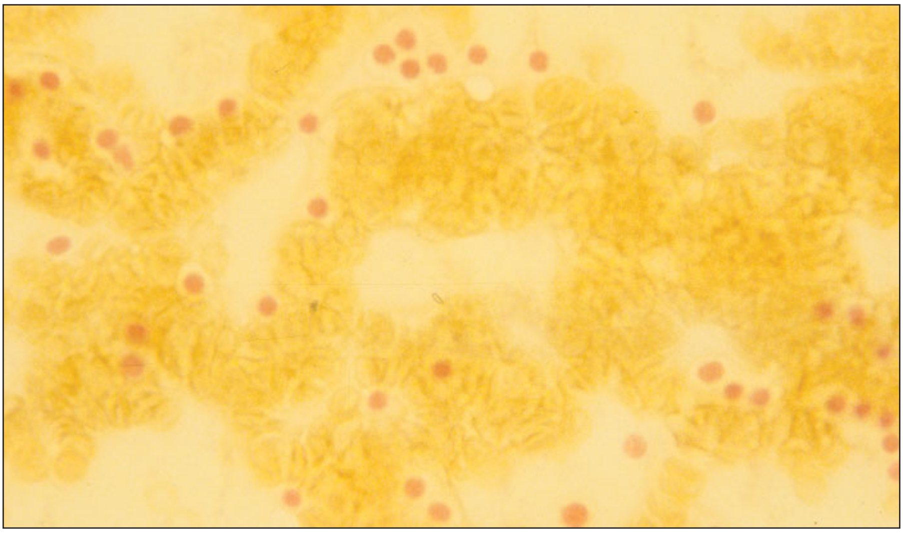


Figure IC1-11

Negative

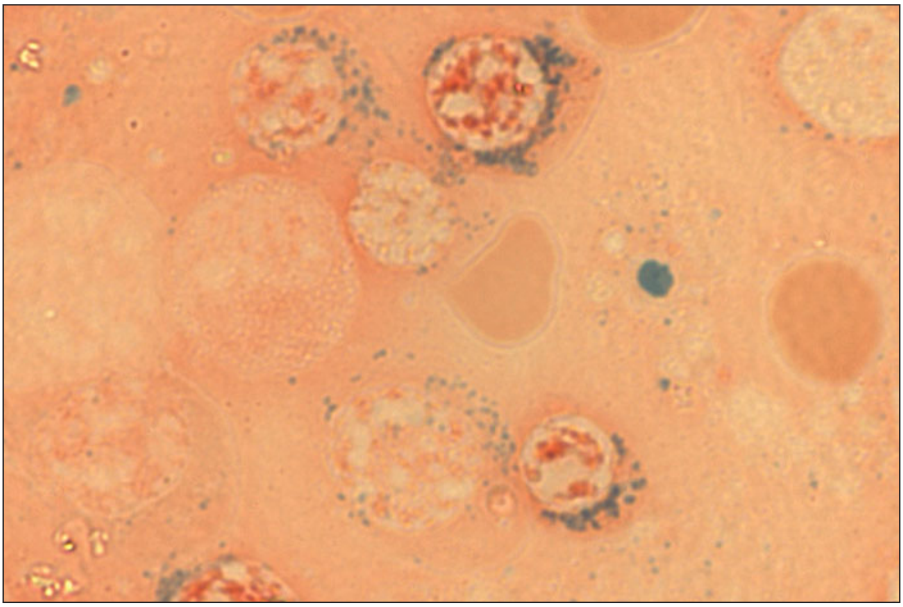


Figure IC1-12

Positive

Cell Type

Erythroblasts, erythrocytes, macrophages, histiocytes

Description

Iron in the form of hemosiderin is normally present in developing normoblasts and in the reticuloendothelial cells of the bone marrow. A Prussian blue color is produced when ferric iron of hemosiderin reacts with an acid ferrocyanide solution to form ferric ferrocyanide.

Positivity or the presence of iron is indicated by the presence of blue to blue-green granules

May be used to determine the presence of iron stores in the marrow

May be used to demonstrate increased numbers of sideroblasts or the presence of pathologic ferric iron located in mitochondria of the erythroblast (ringed sideroblast)

Clinical Conditions

- Myelodysplastic syndromes
- Acute erythroleukemia (M6) (FAB)
- Thalassemias
- Intramacrophage iron is decreased in iron deficiency and increased in hemochromatosis and anemia of chronic diseases

ACID ELUTION (KLEIHAUER-BETKE STAIN)

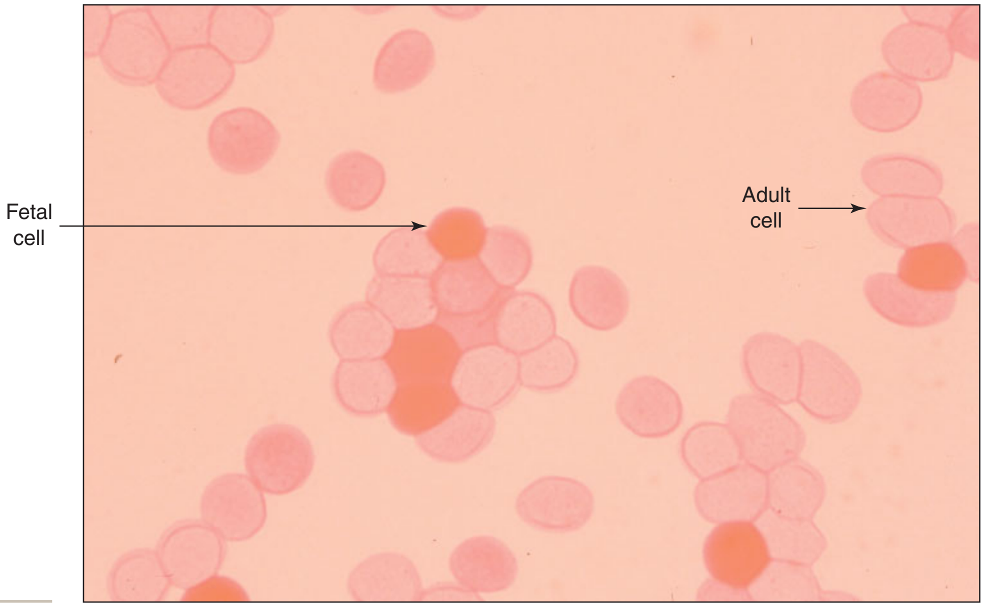


Figure IC1-13

Cell Type

Red blood cells

Description

Cells containing hemoglobin F will appear pink to red

Cells containing no hemoglobin F will have only their outer membrane visible (ghost cells)

Clinical Conditions

- Hereditary persistence of fetal hemoglobin
- Myelodysplastic syndromes
- Some leukemias

LEUKOCYTE ALKALINE PHOSPHATASE STAIN

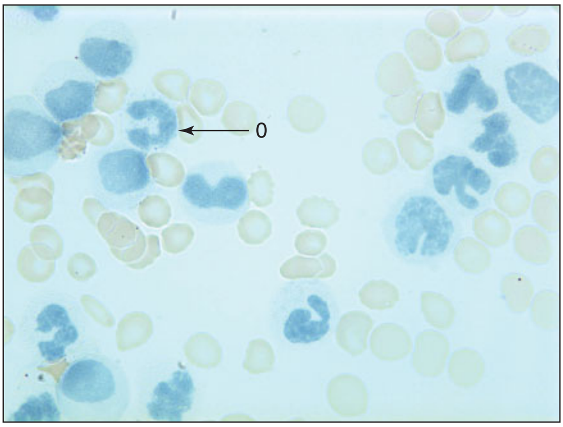


Figure IC1-14

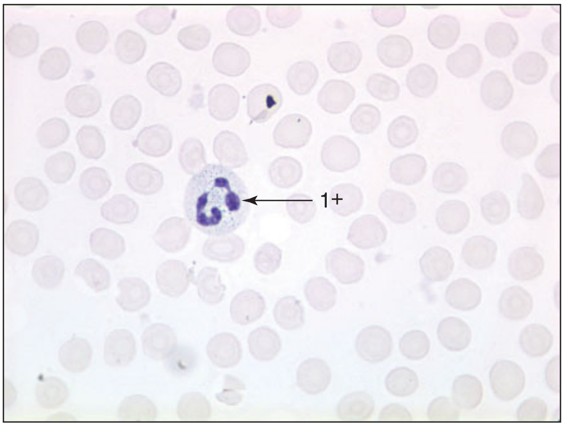


Figure IC1-15

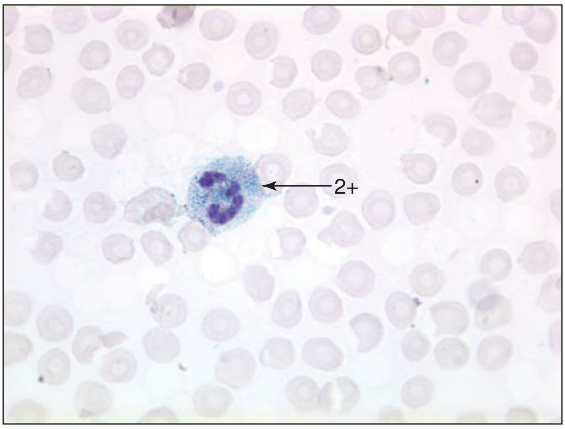


Figure IC1-16

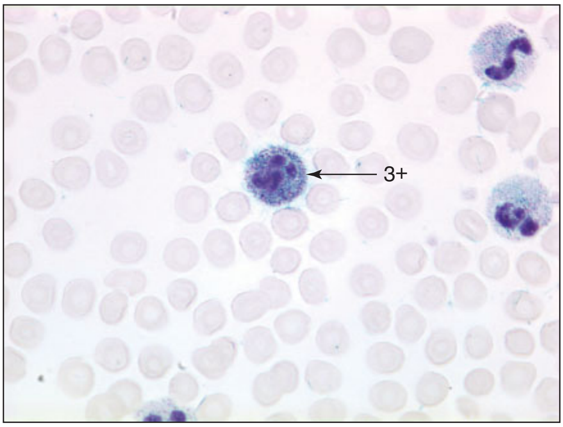


Figure IC1-17

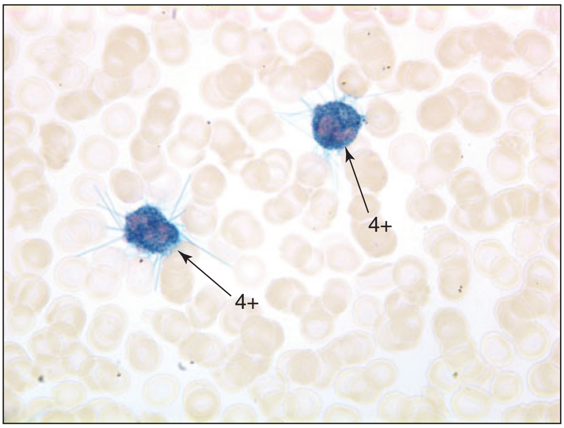


Figure IC1-18

Cell Type

Granulocyte distinguishes leukemoid reaction from chronic myelogenous leukemia

Description

LAP is an enzyme associated with the specific granules

Presence of leukocyte alkaline phosphatase activity indicates intracellular metabolic activity

Positivity is indicated by either a ruby red color or a blue-purple color

Positivity is quantitated

100 consecutive bands or segmented neutrophils are scored using the following criteria:

0	Colorless
1	Diffuse positivity; occasional granules
2	Diffuse positivity; moderate numbers of granules
3	Strong positivity; numerous granules
4	Very strong positivity; dark, confluent granules

The scores of the 100 cells are summed

Clinical Conditions

Increased:

- Leukemoid reaction
- Polycythemia vera
- Pregnancy
- Infections
- Chronic myelocytic leukemia blast crisis
- Myelofibrosis

Decreased:

- Chronic myelogenous leukemia
- Paroxysmal nocturnal hemoglobinuria
- Some myelodysplastic syndromes due to degranulation

NEW METHYLENE BLUE AND BRILLIANT CRESYL BLUE STAINS

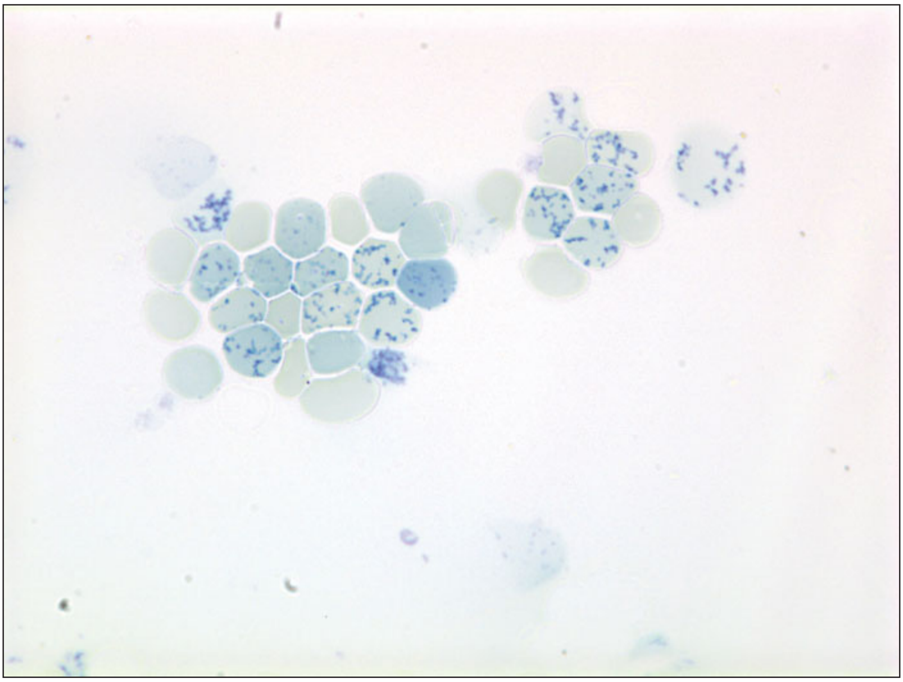


Figure IC1-19

Cell Type

Red blood cells

Description

Supravital stains commonly used in demonstrating aggregates of RNA in immature erythrocytes (reticulocytes)

Pappenheimer bodies, Howell-Jolly bodies, and Heinz bodies are also stained

Clinical Conditions

- Hemolytic anemias
- Folate deficiency
- Vitamin B_{12} deficiency
- Glucose-6-phosphate dehydrogenase deficiency
- Hb H disease
- Myelodysplastic syndromes

PERIODIC ACID-SCHIFF REACTION

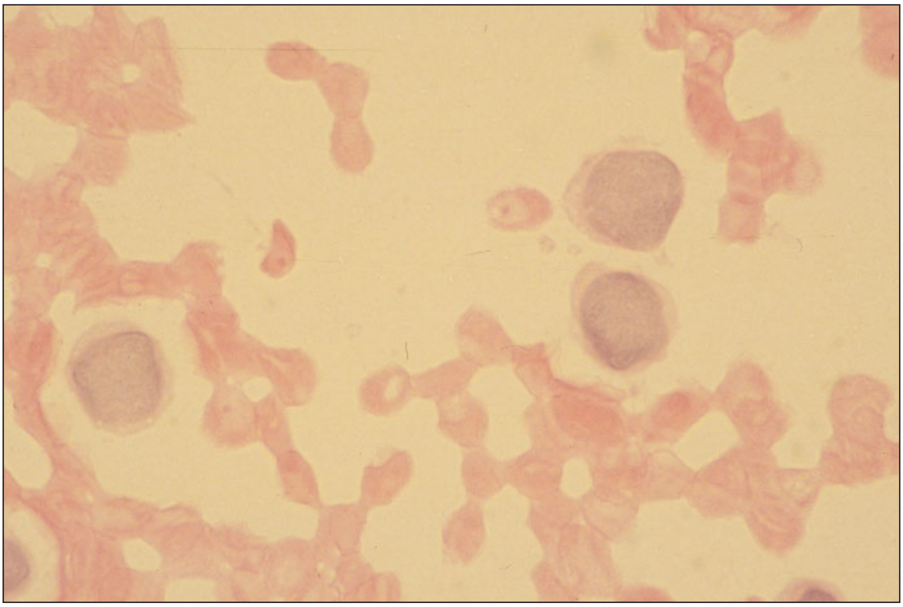


Figure IC1-20

Negative

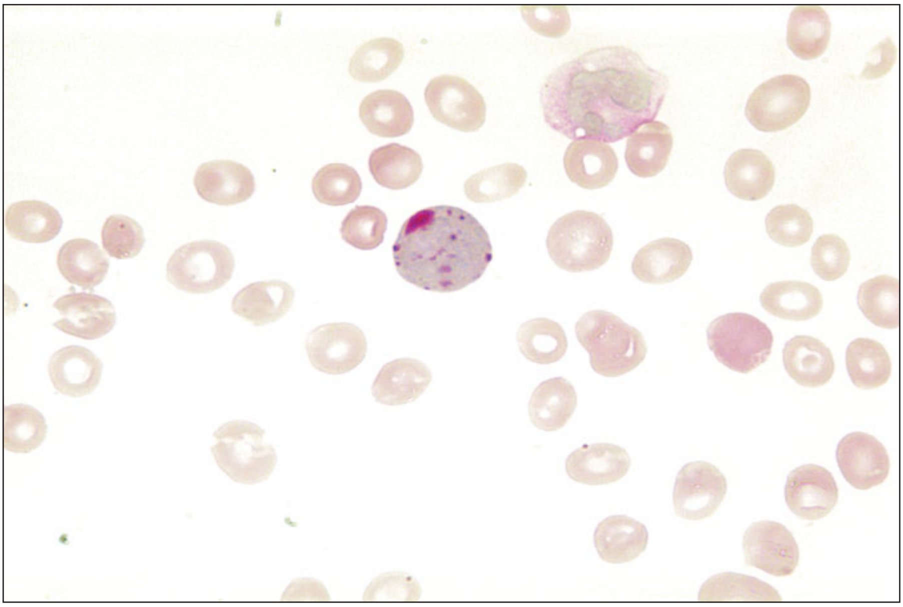


Figure IC1-21

Positive

Cell Type

Neoplastic erythroblasts, granulocytes, monocytes, lymphoblasts, and megakaryocytes (most hematopoietic cells in variable quantities)

Description

PAS stains glycogen
Positivity is indicated by a bright pink color
Lymphocytes, granulocytes, monocytes, and megakaryocytes may be positive
Normal erythroblasts are negative

Clinical Conditions

- Acute erythroleukemia (positive)
- Thalassemia, iron deficiency, sideroblastic anemia (may be positive)
- Burkitt lymphoma cells (negative) (L3)
- Acute lymphocytic leukemia (may have block positivity) (L1, L2)
- Any severe dyserythropoiesis
- Acute myelomonocytic leukemia with abnormal bone marrow eosinophils (granules are positive in the abnormal eosinophils)

PEROXIDASE STAIN

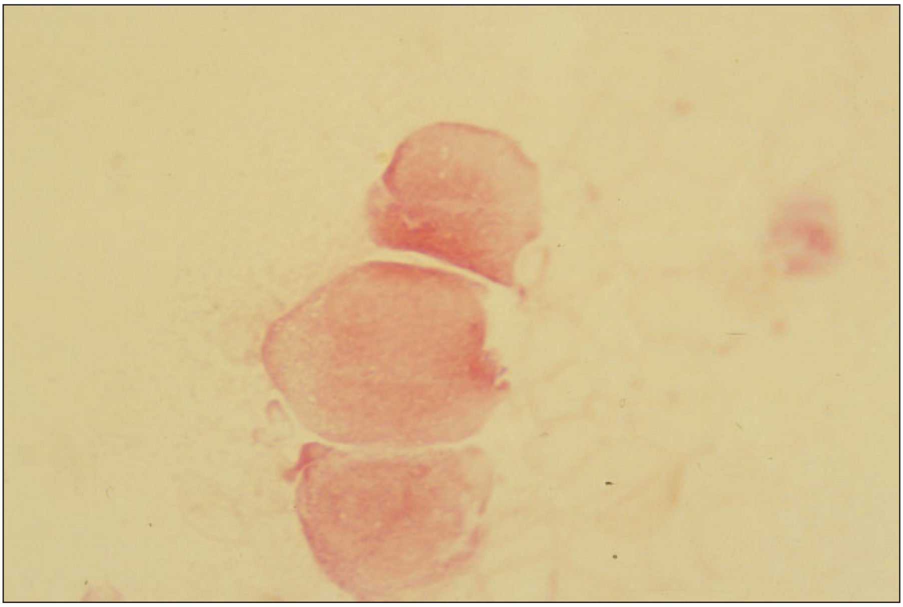


Figure IC1-22

Negative

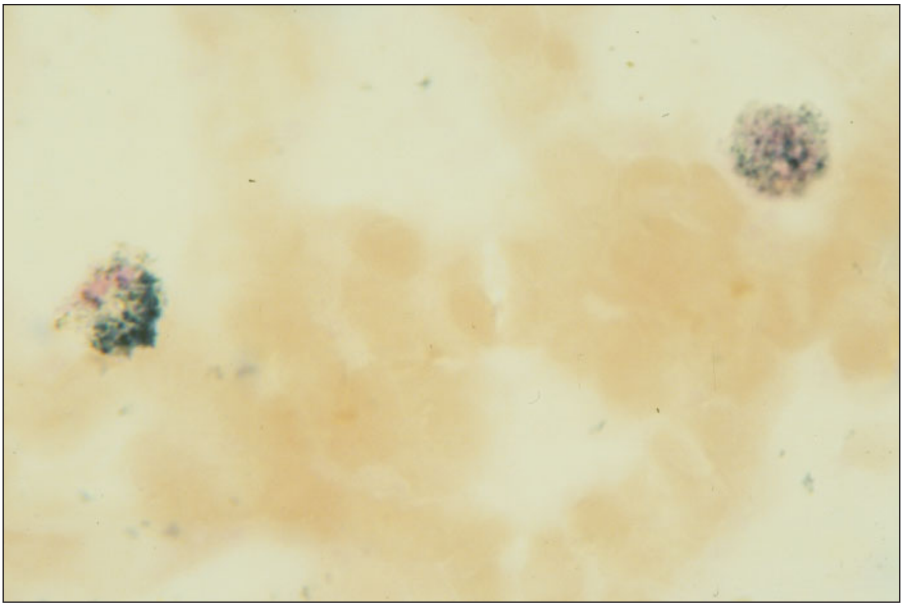


Figure IC1-23

Positive

Cell Type

Myeloid cells—primary granules of the neutrophilic and eosinophilic series, monocytes are faintly positive

Description

Myeloperoxidase is an enzyme capable of oxidizing dye substrates in the presence of hydrogen peroxide

Positivity is indicated by the presence of black or red-brown granules (color depends on the substrate)

Positivity is found in some myeloblasts, promyelocytes, myelocytes, metamyelocytes, neutrophils, eosinophils, and faintly positive in monocytes

Early myeloblasts, basophils, plasma cells, and lymphocytic cells and erythroid cells are negative

Clinical Conditions

- Acute myelocytic leukemia without maturation (M1) (FAB)
- Acute myelocytic leukemia with maturation (M2) (FAB)
- Acute promyelocytic leukemia (M3) (FAB)
- Acute myelomonocytic leukemia (M4) (FAB)
- Erythroleukemia (M6a) (FAB)
- AML with recurrent genetic abnormalities (WHO)
  AML with t(8;21)
  AML with t(15;17)
  AML with inv 16 or t(16;16)

SUDAN BLACK B STAIN

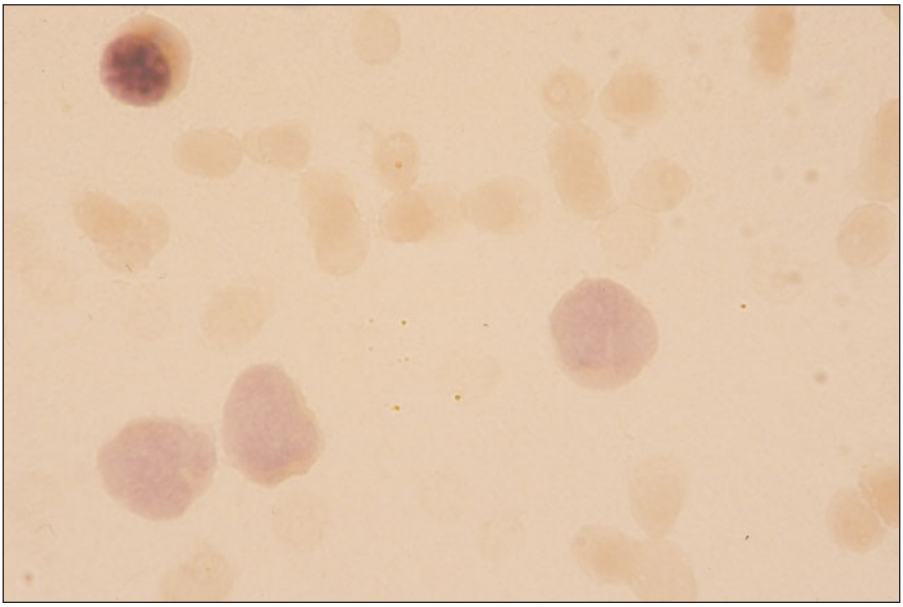


Figure IC1-24

Negative

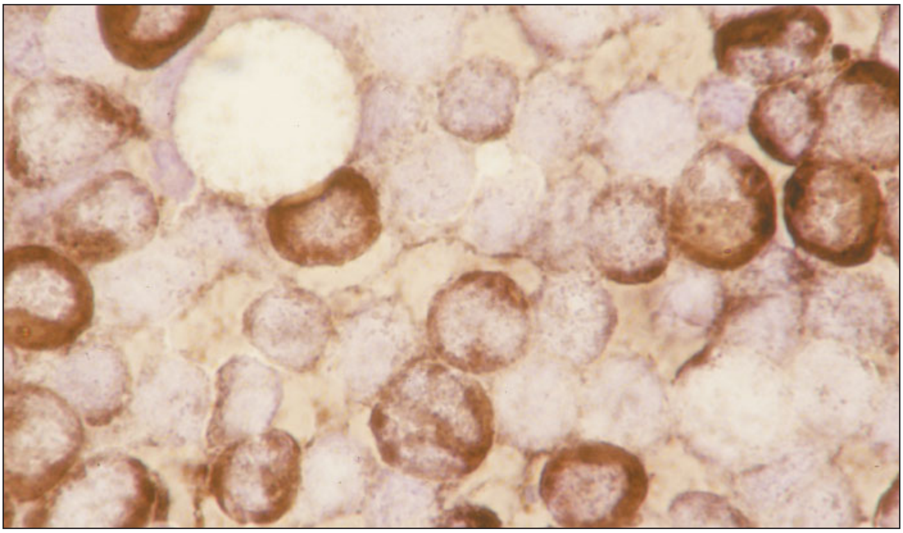


Figure IC1-25

Positive

Cell Type

Neutrophilic and eosinophilic cells and their precursors, monocytes are weakly positive

Description

Separates AML from acute lymphocytic leukemia (ALL)

Sudan black B stains lipid particles found in primary and secondary granules, as well as giving a weak positivity in lysosomal granules found in the monocytic cells

Lymphocytes may rarely have these granules

Positivity is indicated by a brownish-black–colored granule

Clinical Conditions

- Acute myelocytic leukemia without maturation (M1) (FAB)
- Acute myelocytic leukemia with maturation (M2) (FAB)
- Acute promyelocytic leukemia (M3) (FAB)
- Acute myelomonocytic leukemia (M4) (FAB)
- Acute monoblastic leukemia (M5a) (FAB) (if myeloblasts are present)
- Acute monocytic leukemia (M5b) (FAB) (if myeloblasts are present)
- Erythroleukemia (M6a) (FAB) (if myeloblasts are present)
- AML with recurrent genetic abnormalities (WHO)
  AML with t(8;21)
  AML with t(15;17)
  AML with inv 16 or t(16;16)

TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE REACTION

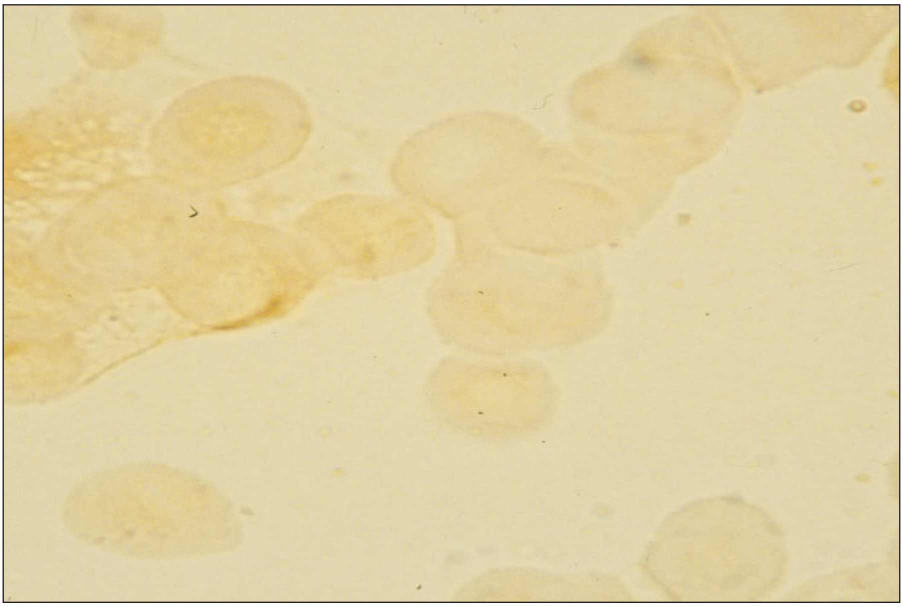


Figure IC1-26

Negative

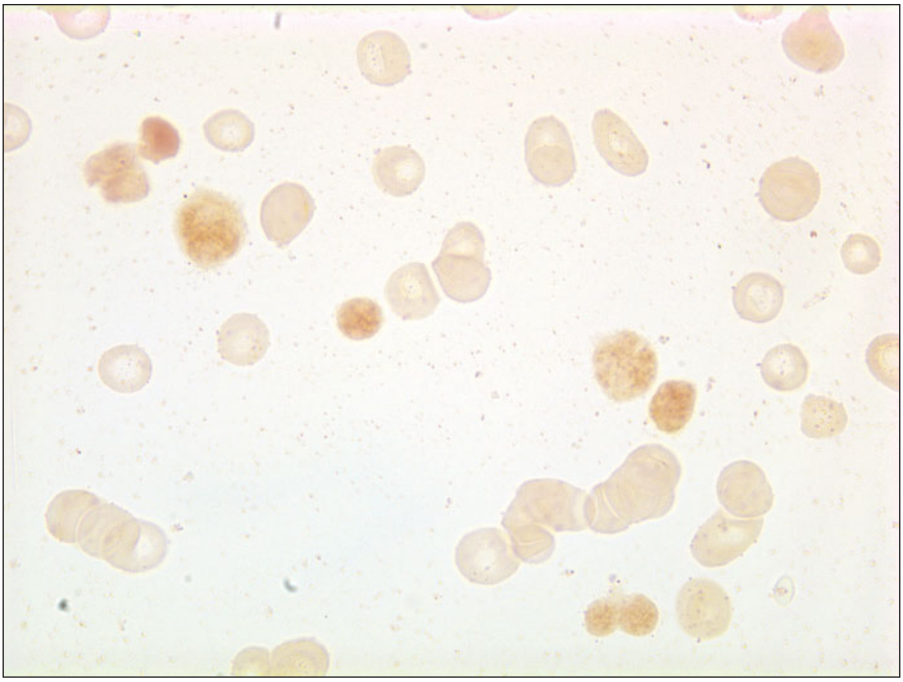


Figure IC1-27

Positive

Cell Type

Primitive lymphocytic cells and neoplastic cells

Description

Enzyme (DNA polymerase) found in the nucleus

Demonstrated through immunofluorescent or immunoperoxidase procedures

Positivity is demonstrated by a lime-green fluorescence or red to brownish-red staining

Clinical Conditions

- T-cell acute lymphoblastic leukemia
- Precursor B-cell acute lymphocytic leukemia
- Lymphoblastic lymphoma
- Chronic myelocytic leukemia with lymphoblastic transformation

TOLUIDINE BLUE STAIN

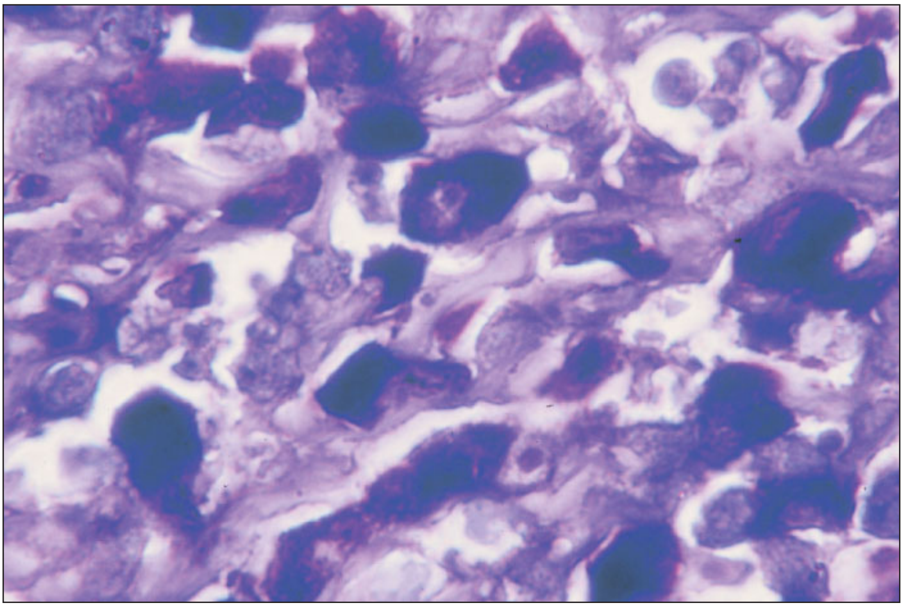


Figure IC1-28

Cell Type

Basophils and mast cells

Description

Reacts with acid mucopolysaccharides (heparan sulfate) to form metachromatic granules

Positivity is indicated by a red-violet color

May not be positive in neoplastic disorders involving these cells

Clinical Conditions

- Mast cell disease
- Basophilic leukemias

RETICULIN STAIN

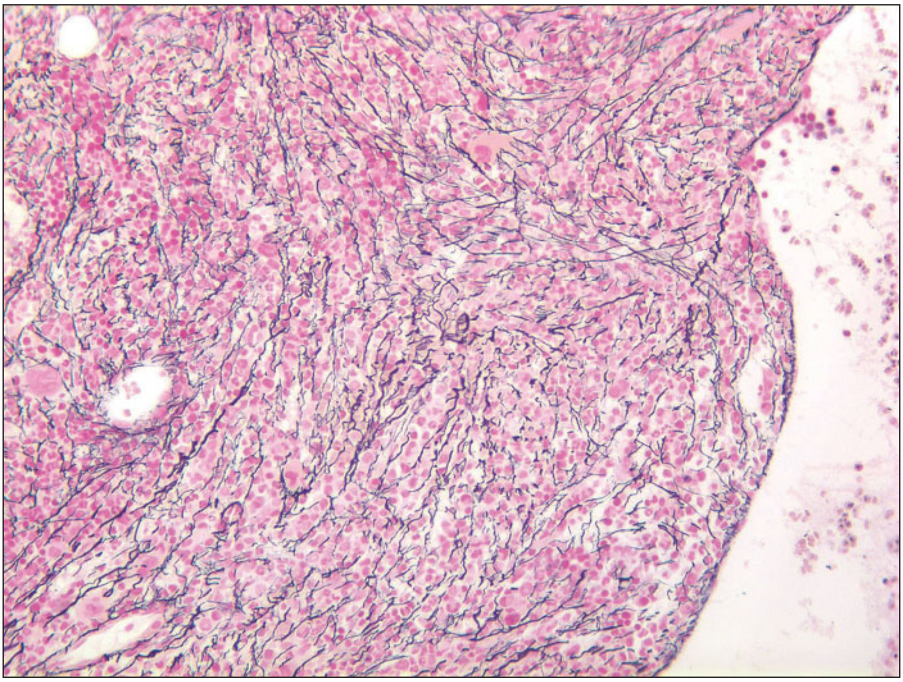


Figure IC1-29

Cell Type

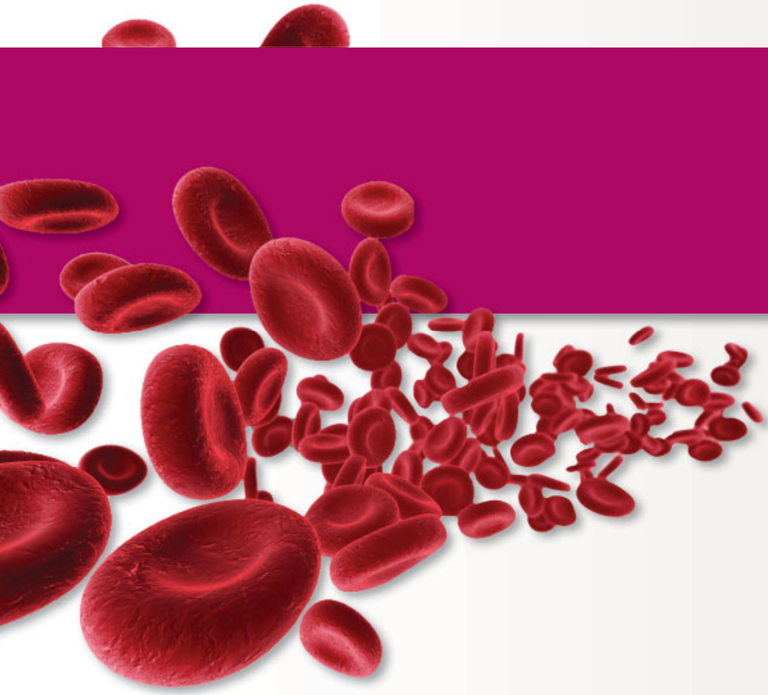
New formed collagen

Description

The newly formed collagen is not cross-linked and stains in the biopsy sections

Clinical Conditions

- Elevated numbers of megakaryocytes
- Myeloproliferative disorders
- Lymphomas (follicular and Hodgkin)
- Megakaryocytic leukemia
- Hairy cell leukemia



Unit II

Hematologic Disorders

- *Section A* Red Blood Cell Disorders
- *Section B* White Blood Cell Disorders
- *Section C* Miscellaneous Disorders

Section A

Red Blood Cell Disorders

CHAPTER 1

Erythrocytosis

POLYCYTHEMIA VERA

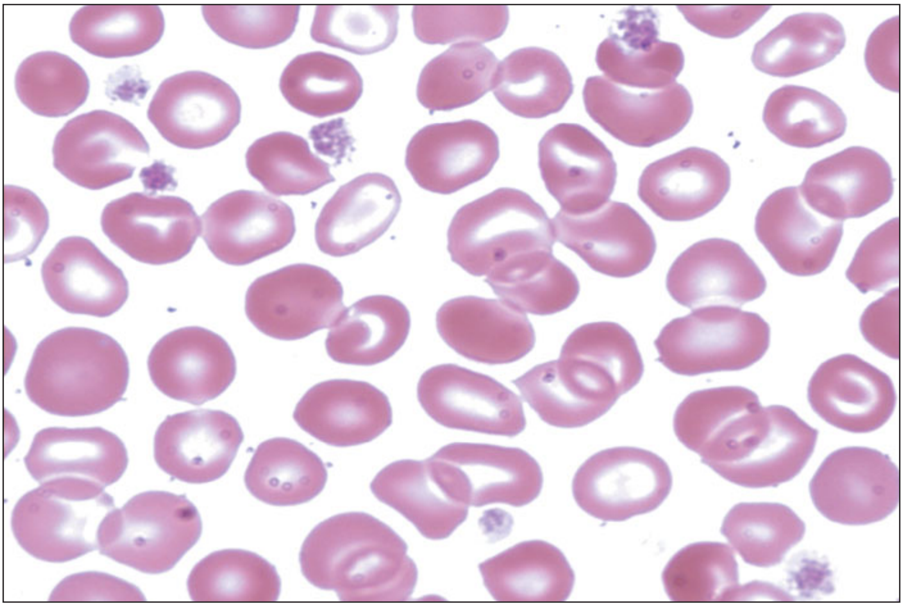


Figure IIA1-1

Peripheral blood smear.

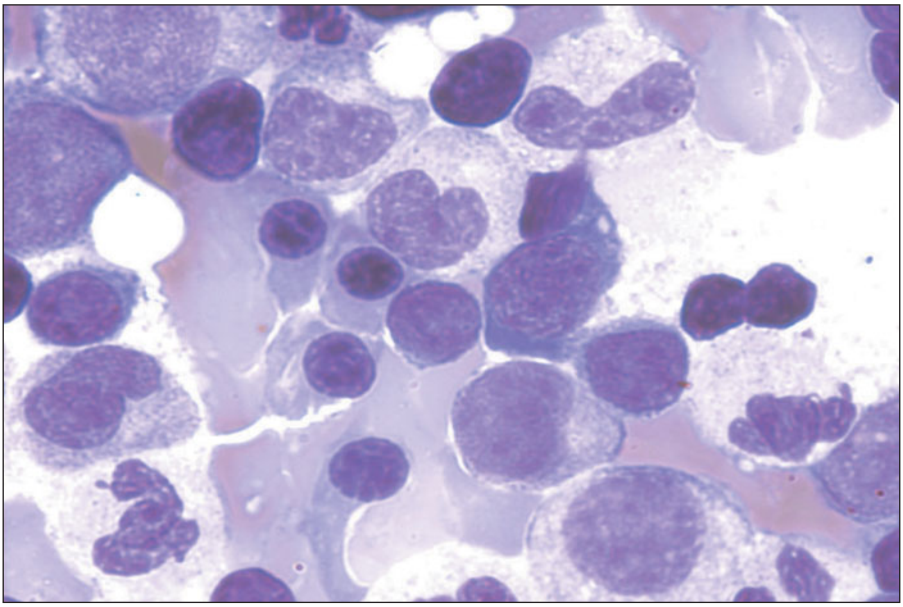


Figure IIA1-2

Bone marrow smear.

Clinical Features

- Usually diagnosed in persons aged 55–70 years
- Slight male predominance
- Headache, confusion, altered mental status, dizziness, visual changes, tinnitus, paresthesias
- Weight loss, epigastric pain, gout, pruritus, thrombosis, and hemorrhage
- Plethora, hypertension, and a mild to moderate degree of splenomegaly and hepatomegaly

Pathology

- Malignancy
- Excessive bone marrow production of red blood cells and an increase in total red blood cell volume
- White blood cell and platelet counts may also increase to a lesser extent
- Increased blood viscosity
- Thrombosis is a complication in more than half of the cases
- Myelofibrosis or acute myeloid leukemia may develop
- Polycythemic stage
- Increased red blood cell mass
- "Spent" phase and postpolycythemic myelofibrosis and myeloid metaplasia
- Anemia
- Bone marrow fibrosis
- Extramedullary hematopoiesis
- Hypersplenism

Laboratory Features

White Blood Cells

- Increased in about two-thirds of patients
- Immature forms usually not seen
- Eosinophils and basophils may be increased
- Leukocyte alkaline phosphatase increased in three-quarters of cases

Platelets

- Normal to increased

Red Blood Cells

- Hemoglobin level increased
- Hematocrit level increased
- Red blood cell mass increased

Bone Marrow

- Hyperplastic
- Erythroid hyperplasia
- Increased megakaryocytes
- Granulocytic hyperplasia
- Increased reticulin in postpolycythemic myelofibrosis and myeloid metaplasia
- Iron stores are often depleted

Traditional Criteria for Diagnosis

Meet three major criteria or two major and two minor criteria

Major criteria

- Increased red blood cell mass
- Splenomegaly
- Normal oxygen level

Minor criteria

- Platelet count >400 × 10^9/L
- White blood cell count >12 × 10^9/L
- Elevated leukocyte alkaline phosphate level
- Elevated vitamin B_{12} level or unbound vitamin B_{12} binding capacity

World Health Organization Criteria for Diagnosis

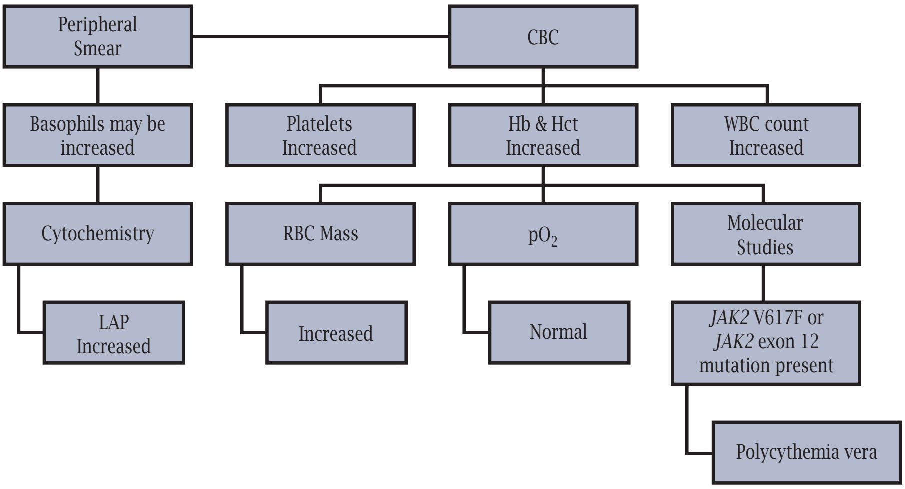
Major Criteria

- Hemoglobin greater than 18.5 g/dL in men, 16.5 g/dL in women or other evidence of increased red cell volume
- Presence of *JAK2* V617F or other functionally similar mutation such as *JAK2* exon 12 mutation

Minor Criteria

- Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic and megakaryocytic proliferation
- Serum erythropoietin level below the reference range for normal
- Endogenous erythroid colony formation *in vitro*

Diagnostic Scheme


Peripheral Smear
CBC
Basophils may be increased
Platelets Increased
Hb & Hct Increased
WBC count Increased
Cytochemistry
RBC Mass
pO$_2$
Molecular Studies
LAP Increased
Increased
Normal
JAK2 V617F or *JAK2* exon 12 mutation present
Polycythemia vera

RELATIVE POLYCYTHEMIA (GAISBÖCK SYNDROME)

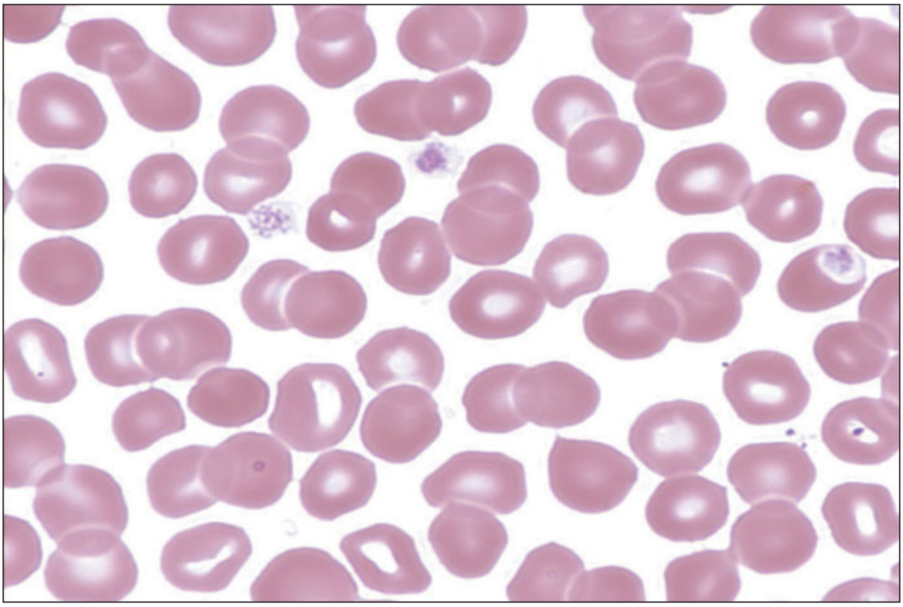


Figure IIA1-3

Peripheral blood smear.

Clinical Features

- Usually occurs in males aged 45–55 years
- The patients tend to be obese, have hypertension, and are heavy smokers

Pathology

- Normal red blood cell mass and clearly decreased plasma volume
- Red blood cell mass at the upper range of normal; plasma volume at the lower range of normal
- Cause of the low plasma volume is not understood but may be related to a variety of causes, including emotional stress, alcoholism, heavy smoking, chronic anxiety, and hypertension

Laboratory Features

White Blood Cells

- Not remarkable

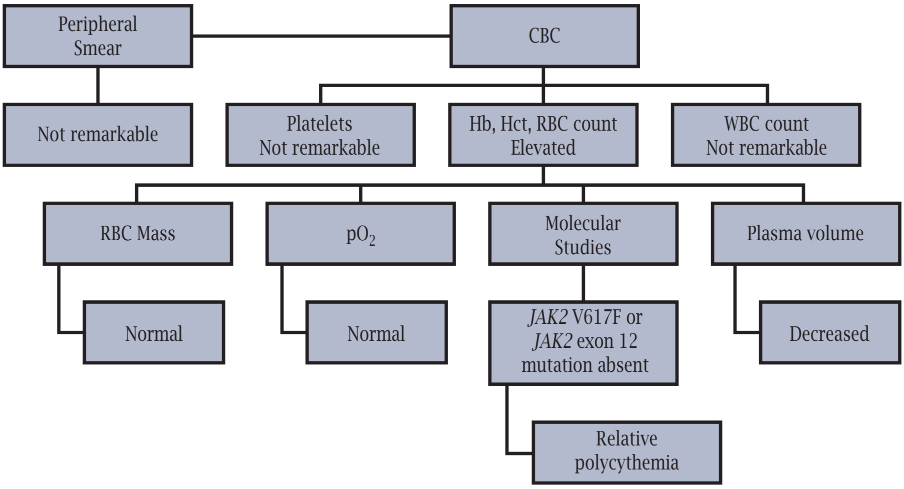
Platelets

- Not remarkable

Red Blood Cells

- Hemoglobin level increased
- Hematocrit level increased
- Red blood cell count increased
- Red blood cell mass normal
- Plasma volume decreased
- Oxygen pressure normal
- Erythropoietin level normal

Diagnostic Scheme


Peripheral Smear
CBC
Not remarkable
Platelets Not remarkable
Hb, Hct, RBC count Elevated
WBC count Not remarkable
RBC Mass
pO$_2$
Molecular Studies
Plasma volume
Normal
Normal
JAK2 V617F or *JAK2* exon 12 mutation absent
Decreased
Relative polycythemia

SECONDARY POLYCYTHEMIA

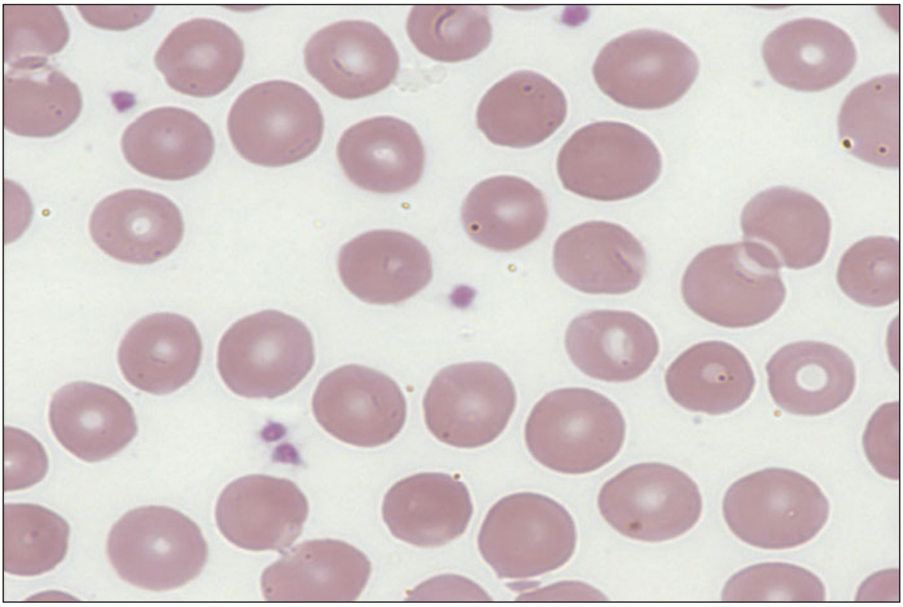


Figure IIA1-4

Peripheral blood smear.

Clinical Features

- Related to the actual cause of the erythrocytosis
- May include plethora, headache, dizziness, visual disturbances, fatigue, paresthesias, decreased mental acuity, obesity, and daytime sleepiness

Pathology

- May be secondary to conditions where there is decreased delivery of oxygen to the tissues, which results in the release of erythropoietin—appropriate secretion of erythropoietin
- May occur in conditions in which delivery of oxygen to the tissues is normal—inappropriate secretion of erythropoietin
- Conditions associated with appropriate secretion of erythropoietin
  - Living at a high altitude
  - High-affinity hemoglobins (e.g., Hb Chesapeake, Rainier, Capetown, Bethesda)
  - Carbon monoxide poisoning
  - Obstructive sleep apnea
  - Drug induced (e.g., testosterone)
  - Obesity-hypoventilation syndrome (Pickwickian)
- Conditions associated with inappropriate secretion of erythropoietin
  - Hepatoma
  - Pheochromocytoma
  - Renal cell cancer, renal cyst, or renal artery stenosis
  - Cerebellar hemangioma

Laboratory Features

White Blood Cells

- Not remarkable

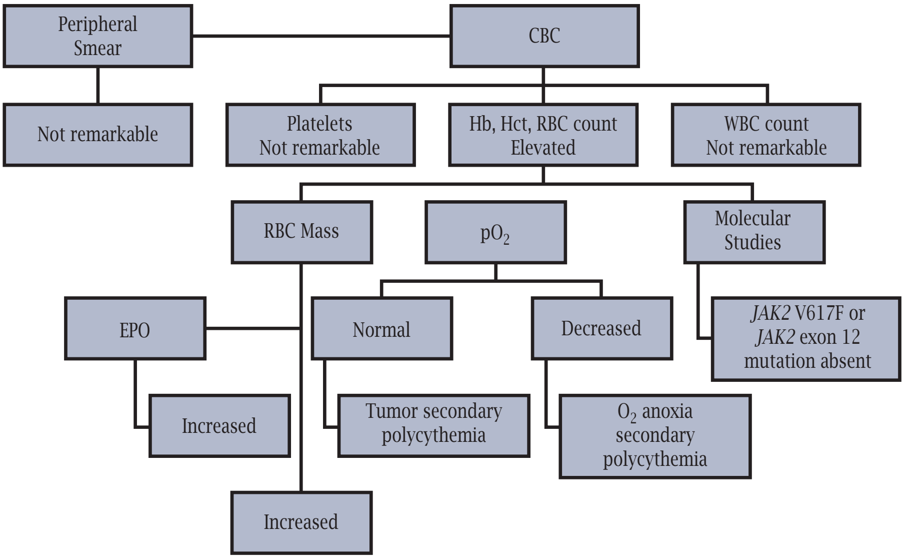
Platelets

- Not remarkable

Red Blood Cells

- Hemoglobin level increased
- Hematocrit level increased
- Red blood cell count increased
- Red blood cell mass increased
- Increased erythropoietin
- Decreased oxygen pressure if due to anoxia; normal oxygen pressure if due to tumor

Diagnostic Scheme


Peripheral Smear
CBC
Not remarkable
Platelets Not remarkable
Hb, Hct, RBC count Elevated
WBC count Not remarkable
RBC Mass
pO2
Molecular Studies
EPO
Normal
Decreased
JAK2 V617F or JAK2 exon 12 mutation absent
Increased
Tumor secondary polycythemia
O2 anoxia secondary polycythemia
Increased

CHAPTER 2

Anemias Due to Disordered Iron Metabolism or Heme Synthesis

ANEMIA OF CHRONIC DISEASE

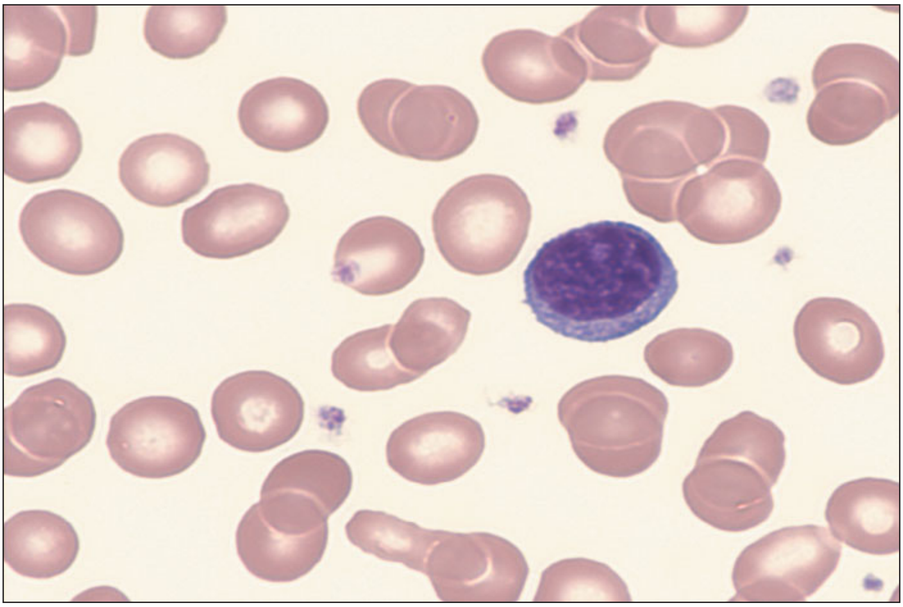


Figure IIA2-1A

Peripheral blood smear.

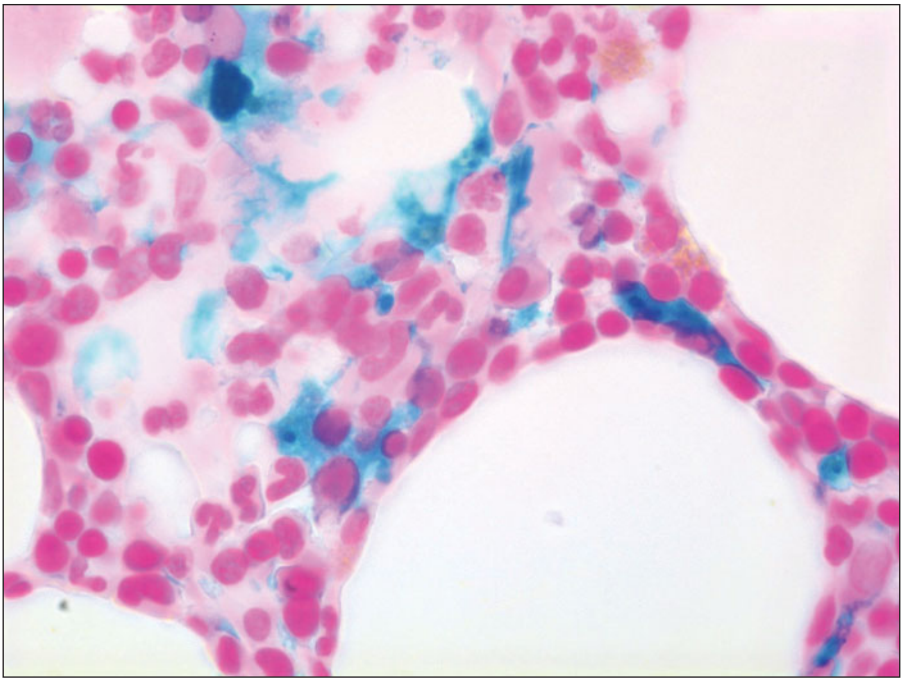


Figure IIA2-1B

Prussian blue stain.

Clinical Features

- Those of the underlying disease: inflammatory, neoplastic, or infectious state

Pathology

- Hypoproliferative anemia
- Impaired release of iron from the reticuloendothelial cells for hemoglobin synthesis
- Decreased red blood cell survival

Laboratory Features

White Blood Cells

- Not consistent—depends on the underlying disease

Platelets

- Not consistent—depends on the underlying disease

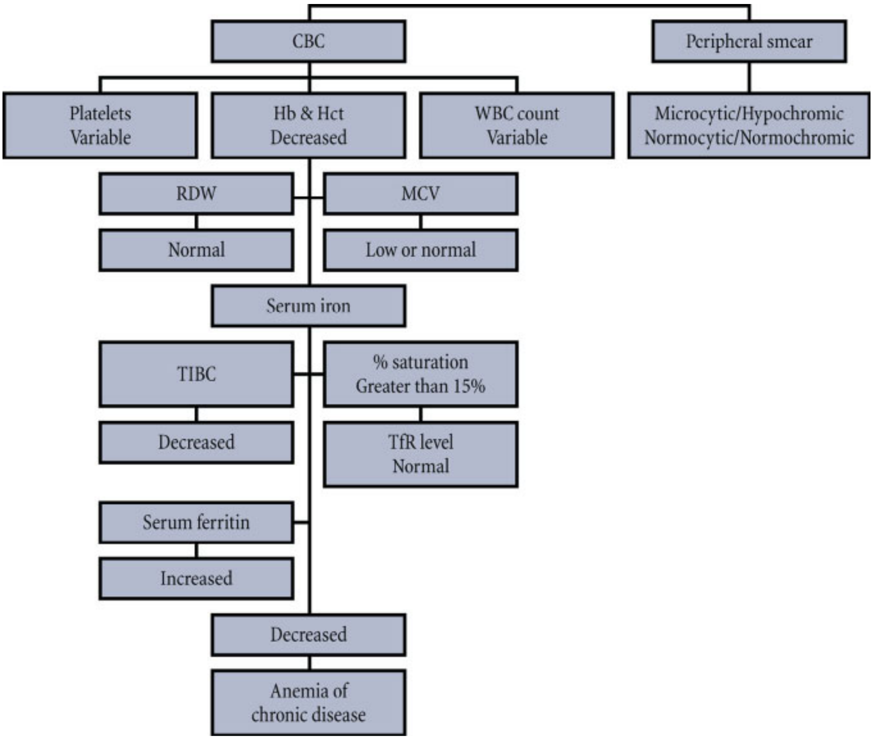
Red Blood Cells

- Decreased hemoglobin and hematocrit
- Normocytic/normochromic anemia
- Microcytic/hypochromic anemia
- Reticulocyte count normal to slightly increased

Bone Marrow

- Normal to increased hemosiderin
- Decreased sideroblasts
- Decreased serum iron level
- Normal or decreased total iron binding capacity
- Decreased % saturation (usually >15%)
- Normal or increased serum ferritin level

Diagnostic Scheme


CBC
Peripheral smear
Platelets Variable
Hb & Hct Decreased
WBC count Variable
Microcytic/Hypochromic Normocytic/Normochromic
RDW
MCV
Normal
Low or normal
Serum iron
TIBC
% saturation Greater than 15%
Decreased
TfR level Normal
Serum ferritin
Increased
Decreased
Anemia of chronic disease

ERYTHROPOIETIC PORPHYRIA (GUNTHER'S DISEASE)

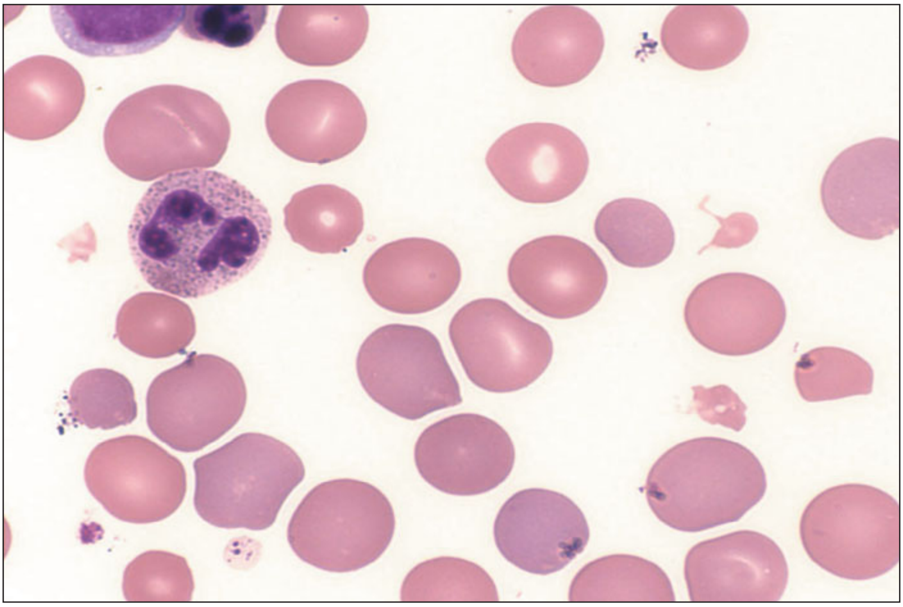


Figure IIA2-2

Peripheral blood smear.

Clinical Features

- Rare autosomal recessive disease
- Appears in infancy
- Urine is pink to reddish-brown
- Vesicular or bullous eruptions appear on exposed areas of the body
- Scarring occurs and may lead to severe deformities of the nose, ears, eyes, and fingers
- Teeth fluoresce
- Hypertrichosis affects the entire body
- Splenomegaly

Pathology

- Decreased tissue uroporphyrinogen III cosynthetase
- Hemolytic anemia

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

Red Blood Cells

- Moderate to severe normocytic/normochromic anemia
- Polychromatophilia
- Nucleated red blood cells in the peripheral blood
- Red blood cells fluoresce
- Increased reticulocyte count
- Excessive porphyrin deposits in the red blood cells

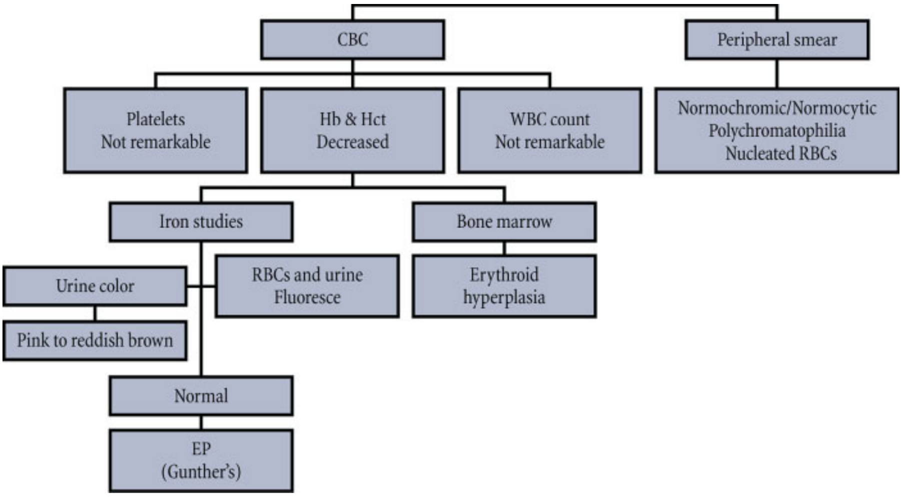
Bone Marrow

- Erythroid hyperplasia
- Normoblasts fluoresce
- Ineffective erythropoiesis

Chemistries

- Normal serum iron level
- Normal serum ferritin level
- Increased unconjugated bilirubin level
- Increased urine and fecal urobilinogen levels
- Excessive amounts of uroporphyrin I and coproporphyrin I in urine and feces

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Decreased
WBC count Not remarkable
Normochromic/Normocytic Polychromatophilia Nucleated RBCs
Iron studies
Bone marrow
Urine color
RBCs and urine Fluoresce
Erythroid hyperplasia
Pink to reddish brown
Normal
EP (Gunther's)

ERYTHROPOIETIC PROTOPORPHYRIA

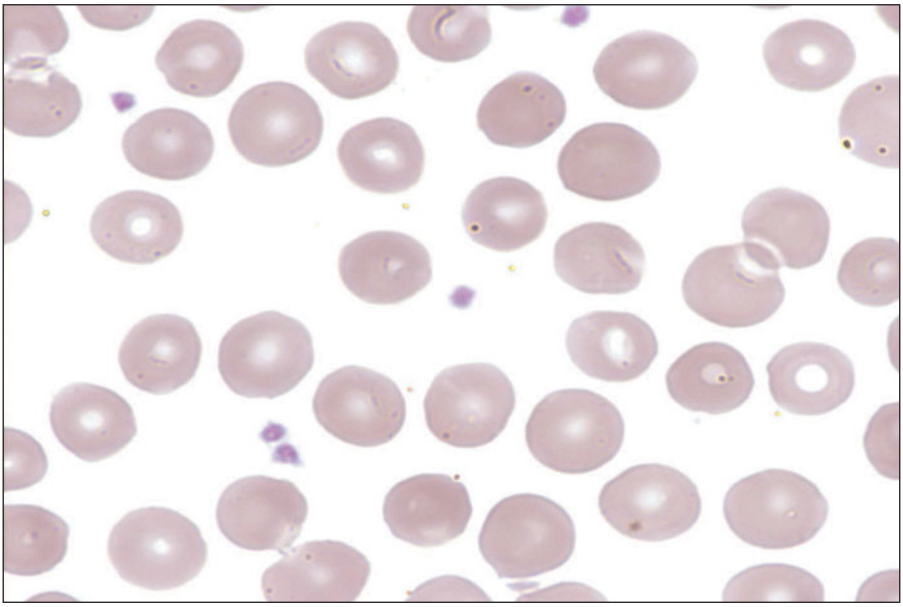


Figure IIA2-3

Peripheral blood smear.

Clinical Features

- Autosomal dominant or recessive transmission
- Usually begins before teen years
- Burning, redness, itching, swelling of skin
- Photosensitivity is not severe
- Relatively mild course

Pathology

- Deficiency of ferrochelatase
- Accumulation of protoporphyrin

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

Red Blood Cells

- No hemolytic anemia
- No abnormalities
- Red blood cells may accumulate protoporphyrins and fluoresce

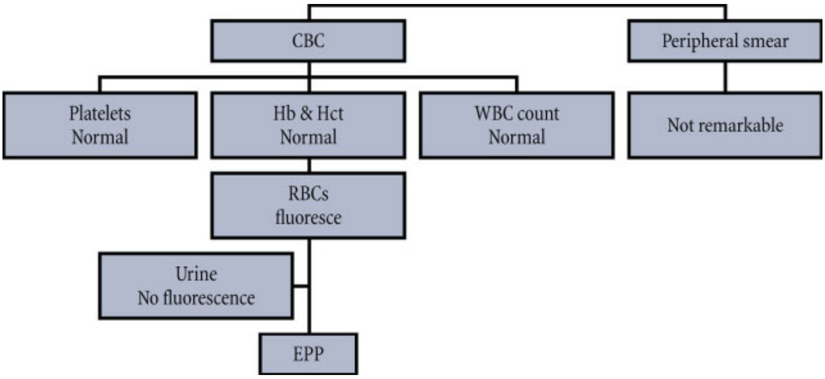
Bone Marrow

- No abnormalities
- The cytoplasm of normoblasts fluoresce intensely

Chemistries

- Increased levels of protoporphyrin found in red blood cells, plasma, and feces but not in urine

Diagnostic Scheme


CBC
Peripheral smear
Platelets Normal
Hb & Hct Normal
WBC count Normal
Not remarkable
RBCs fluoresce
Urine No fluorescence
EPP

IRON DEFICIENCY ANEMIA

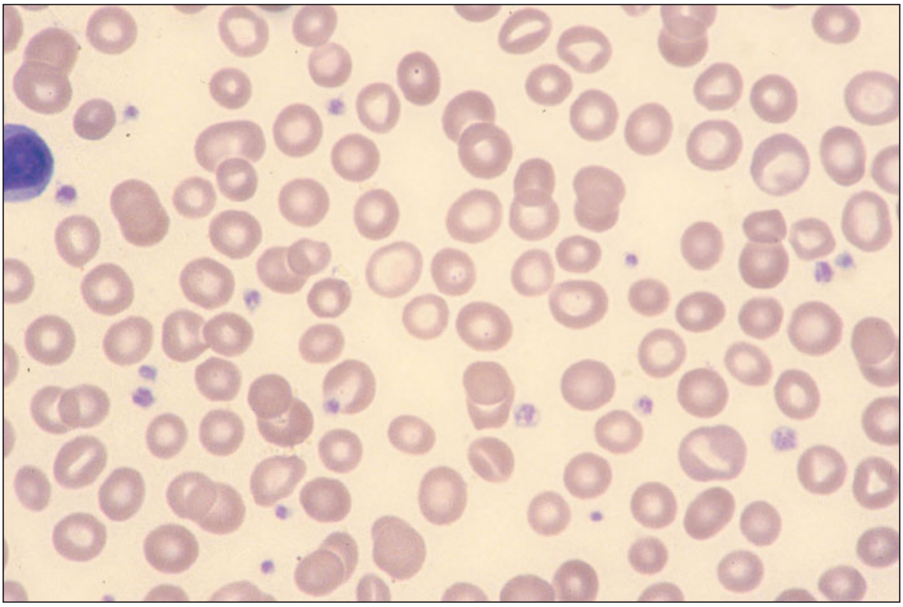


Figure IIA2-4

Peripheral blood smear.

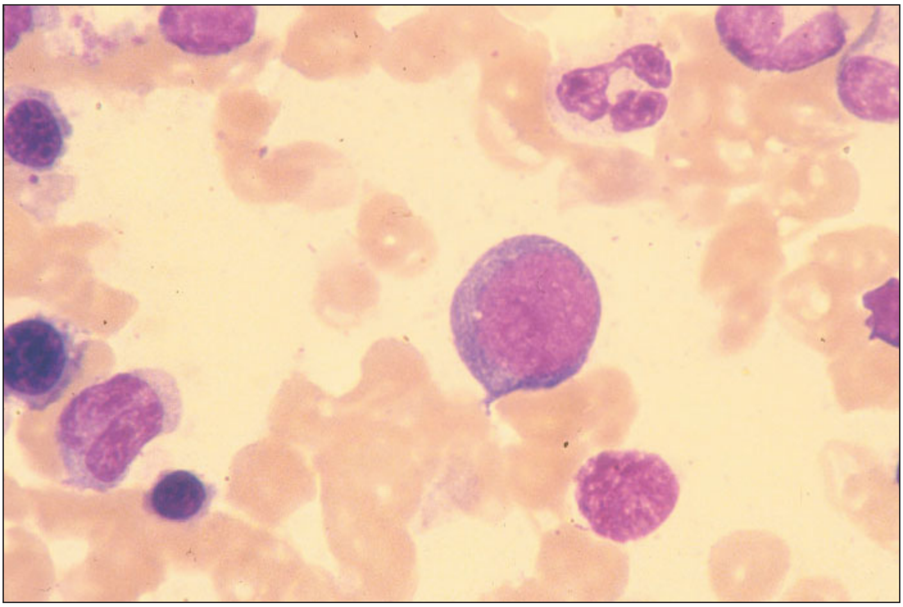


Figure IIA2-5

Bone marrow smear.

Clinical Features

- Fatigue, loss of stamina, exercise intolerance
- Delayed growth
- Lethargy
- Dizziness
- Pallor
- Glossitis
- Koilonychia (spoon-nails)
- Crave dirt or paint (pica) or ice (pagophagia)

Pathology

- Deficient heme synthesis
- Ineffective erythropoiesis
- Increased iron loss
  - Pregnancy
  - Menstruation
  - Chronic blood loss from gastrointestinal tract
- Low availability of iron
  - Rapid growth period
  - Defective gastric function
  - Achlorhydria
  - Gastrectomy

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Normal or slightly increased

Red Blood Cells

- Hemoglobin and hematocrit levels decreased
- Microcytic/hypochromic anemia
- Reticulocyte count normal or slightly increased
- Increased red blood cell distribution width
- Pencil- or cigar-shaped red blood cells, codocytes

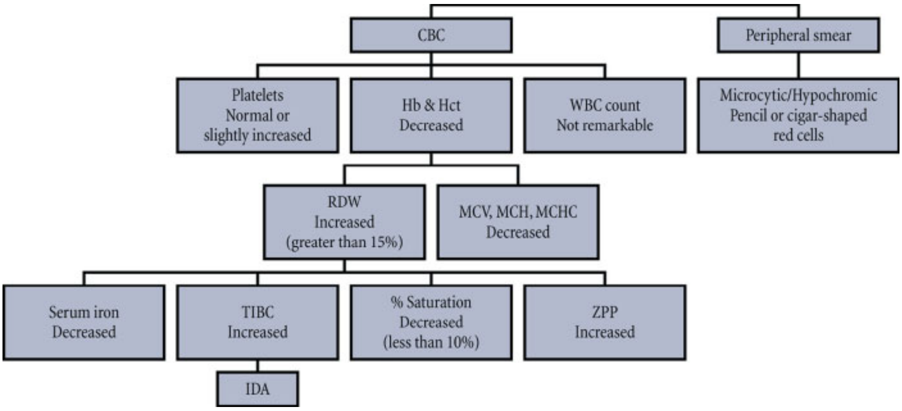
Bone Marrow

- Erythroblastic hyperplasia
- Absent hemosiderin
- Decreased sideroblasts (<10%)
- Erythroblasts are smaller than normal, with ragged rims of cytoplasm containing little hemoglobin

Chemistries

- Decreased serum iron level
- Increased total iron binding capacity
- Decreased % saturation (<15%)
- Decreased serum ferritin level
- Increased zinc protoporphyrin

Diagnostic Scheme


CBC
Peripheral smear
Platelets Normal or slightly increased
Hb & Hct Decreased
WBC count Not remarkable
Microcytic/Hypochromic Pencil or cigar-shaped red cells
RDW Increased (greater than 15%)
MCV, MCH, MCHC Decreased
Serum iron Decreased
TIBC Increased
% Saturation Decreased (less than 10%)
ZPP Increased
IDA

LEAD INTOXICATION (PLUMBISM)

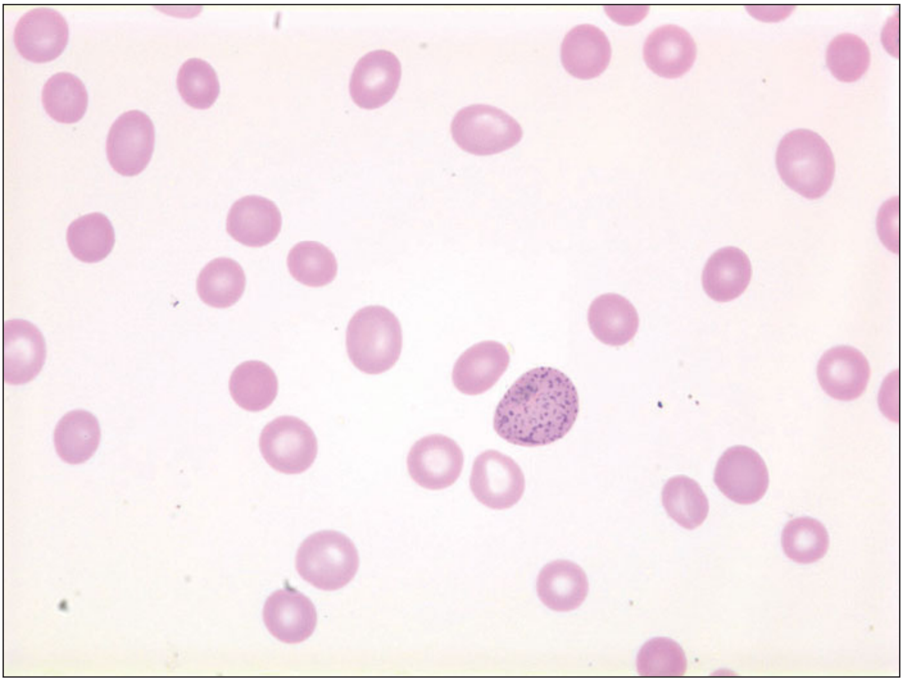


Figure IIA2-6

Peripheral blood smear.

Clinical Features

- Abdominal pain
- Constipation
- Vomiting
- Muscle weakness
- Lead line on gums
- Skin lesions
- Neurologic dysfunctions

Pathology

- Synthesis of heme is impaired
- Interference with iron storage in the mitochondria, which may lead to sideroblastic anemia
- Activity of most enzymes in heme synthesis is inhibited
- Ineffective erythropoiesis (hemolysis because of RNA breakdown)

Laboratory Features

White Blood Cells

- Not consistent findings

Platelets

- Not remarkable

Red Blood Cells

- Microcytic/hypochromic anemia
- Basophilic stippling
- Reticulocyte count normal to increased

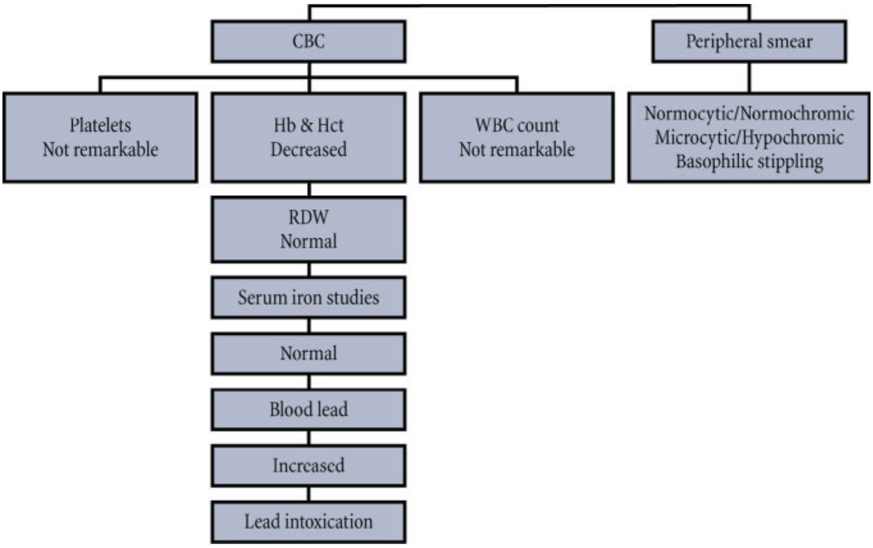
Bone Marrow

- Normal hemosiderin
- Basophilic stippling in normoblasts

Chemistries

- Increased free erythrocyte protoporphyrin
- Normal serum ferritin level
- Increased λ-aminolevulinic acid levels
- Normal porphobilinogen
- Increased blood lead levels

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Decreased
WBC count Not remarkable
Normocytic/Normochromic Microcytic/Hypochromic Basophilic stippling
RDW Normal
Serum iron studies
Normal
Blood lead
Increased
Lead intoxication

SIDEROBLASTIC ANEMIA

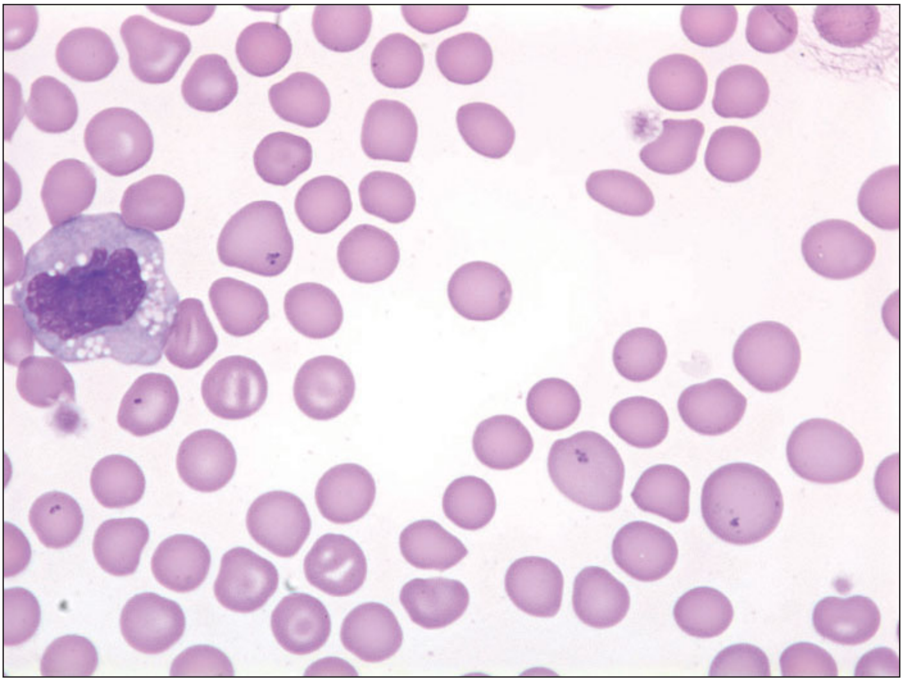


Figure **IIA2-7**

Peripheral blood smear.

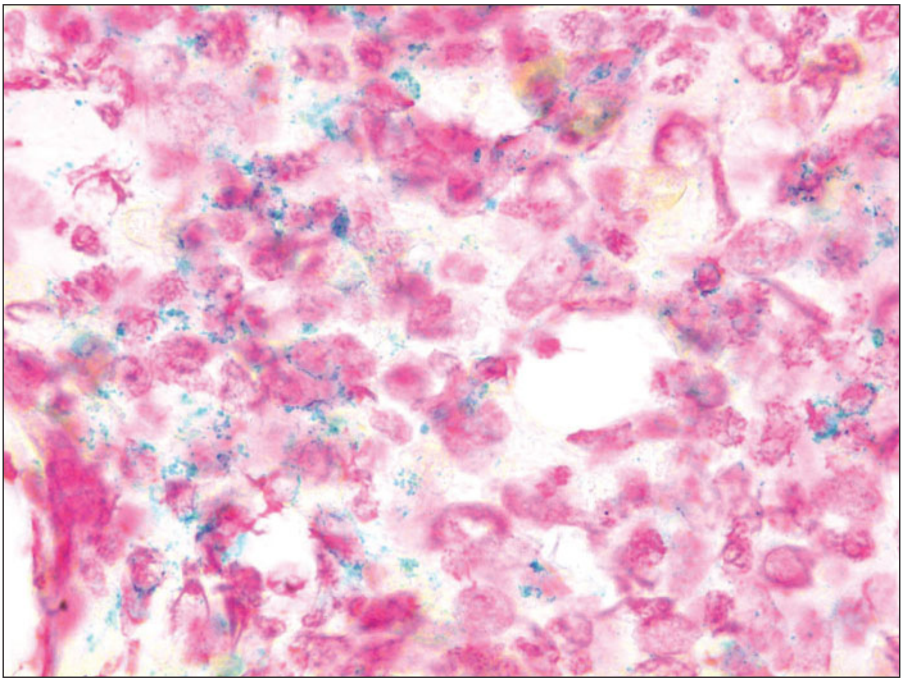


Figure **IIA2-8**

Prussian blue stain.

Clinical Features

- Hepatosplenomegaly
- Two classifications:
  - Inherited
    - Usually sex linked
    - May be autosomal
  - Acquired
    - Idiopathic (a type of myelodysplastic syndrome—refractory anemia with ringed sideroblasts [RARS])
    - Secondary (e.g., drugs)

Pathology

- Common features
  - Ineffective erythropoiesis
  - Increased levels of tissue iron (ringed sideroblasts)
  - Failure of protoporphyrin and heme synthesis due to abnormal enzyme activity
- Inherited
  - Symptoms appear early owing to abnormal heme synthesis enzymes
- Idiopathic
  - Clonal disorder
  - Abnormal red blood cell distribution
  - Abnormal heme synthesis enzymes
- Secondary
  - Drugs
    - Inhibition of enzymes

Laboratory Features

White Blood Cells

- Normal to decreased

Platelets

- Not remarkable

Red Blood Cells

- Commonly microcytic/hypochromic anemia
- Dimorphism
- Increased red blood cell distribution width
- Reticulocyte count normal or slightly increased
- Basophilic stippling
- Pappenheimer bodies

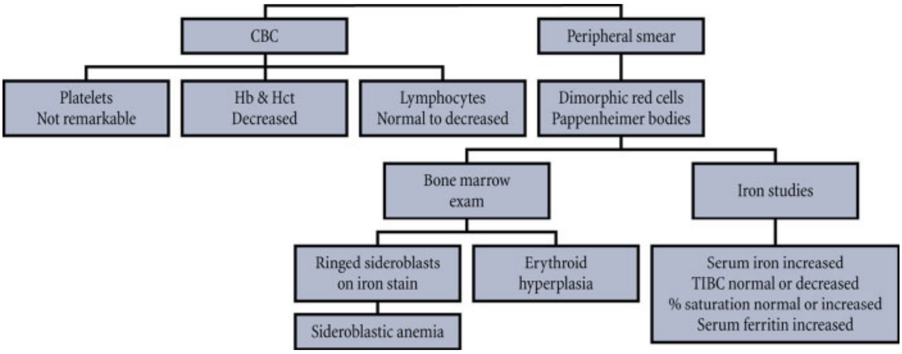
Bone Marrow

- Erythroid hyperplasia
- Large numbers of sideroblasts and ringed sideroblasts

Chemistries

- Increased hemosiderin
- Increased serum iron
- Normal or decreased total iron binding capacity
- Normal or increased % saturation
- Increased serum ferritin level

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Decreased
Lymphocytes Normal to decreased
Dimorphic red cells Pappenheimer bodies
Bone marrow exam
Iron studies
Ringed sideroblasts on iron stain
Erythroid hyperplasia
Serum iron increased
TIBC normal or decreased
% saturation normal or increased
Serum ferritin increased
Sideroblastic anemia

CHAPTER 3

Megaloblastic Anemias

FOLIC ACID DEFICIENCY

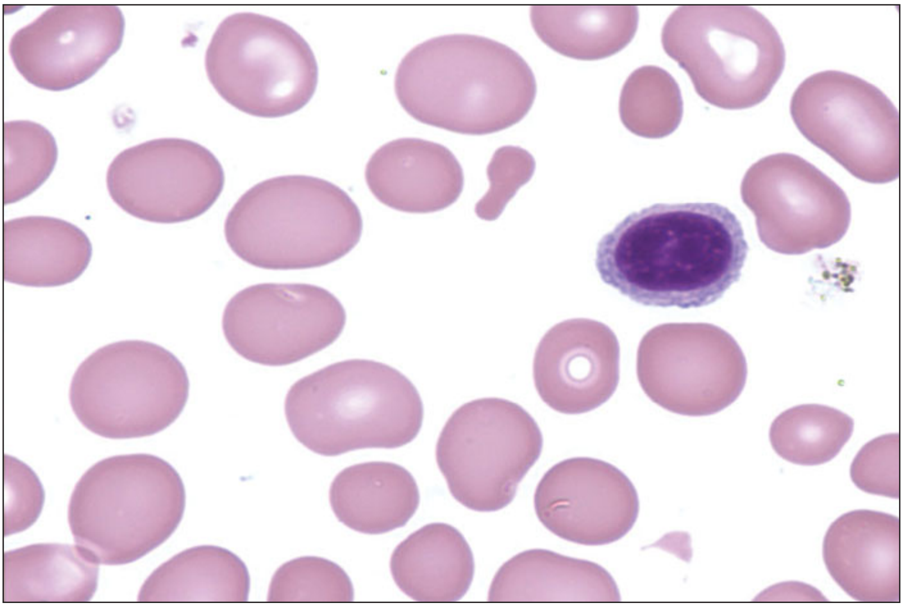


Figure **IIA3-1**

Peripheral blood smear.

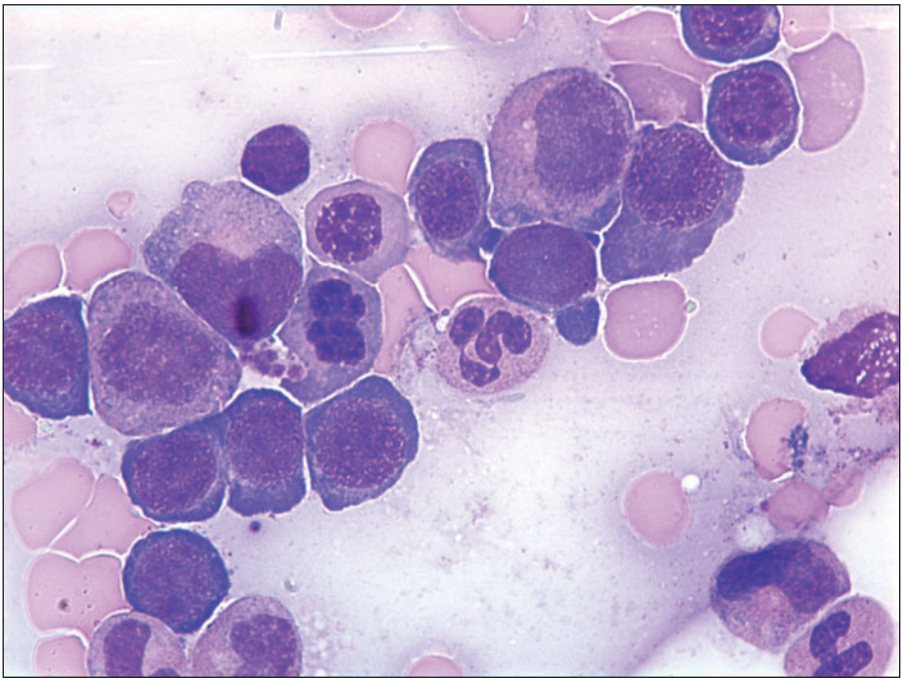


Figure **IIA3-2**

Bone marrow smear.

Clinical Features

- Usually affects the hematopoietic and gastrointestinal systems
- Neurologic system is *not* affected
- Anemia onset may occur 2–3 months after deficiency and may be severe
- History of food faddism, alcoholism, or poor dietary intake
- Glossitis

Pathology

- Defective DNA synthesis due to folate deficiency
  - Ineffective hematopoiesis
  - Dietary deficiency—levels can decrease within 1 month of deficient intake
  - Increased demands—pregnancy
  - Malabsorption
    - Nontropical sprue (gluten-sensitive enteropathy)
    - Tropical sprue
  - Drug therapy
    - Phenytoin
    - Methotrexate

Laboratory Features

White Blood Cells

- Granulocytopenia
- Hypersegmented neutrophils

Platelets

- Thrombocytopenia

Red Blood Cells

- Macrocytic, normochromic anemia
- Presence of macroovalocytes
- Presence of nucleated red blood cells
- Howell-Jolly bodies, Cabot rings, basophilic stippling
- Reticulocyte count normal or decreased
- No polychromasia
- Red blood cell distribution width increased

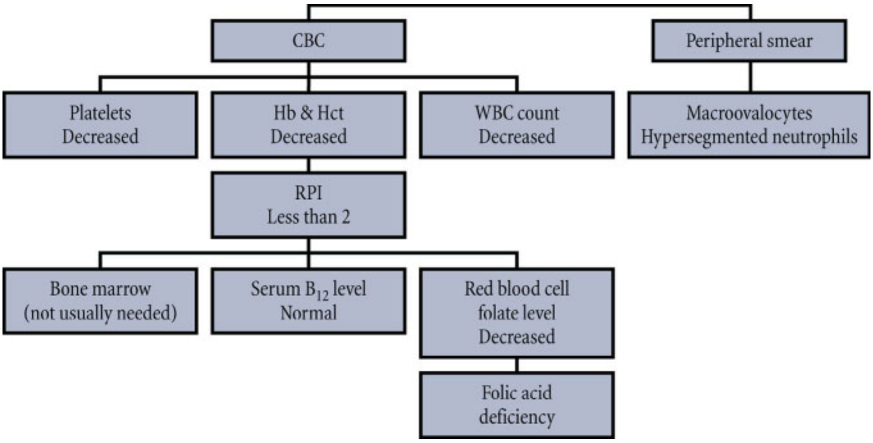
Bone Marrow

- Megaloblastic erythroid precursors
- Giant myelocytes and metamyelocytes may be seen
- Megakaryocytes may exhibit hyperlobulation and are increased in number

Chemistries

- Indirect bilirubin level increased
- Serum lactic dehydrogenase level increased
- Serum folate level decreased
- Red blood cell folate level decreased
- Methylmalonic acid level normal
- Serum B_{12} level normal or decreased
- Homocysteine level increased

Diagnostic Scheme


CBC
Peripheral smear
Platelets Decreased
Hb & Hct Decreased
WBC count Decreased
Macroovalocytes Hypersegmented neutrophils
RPI Less than 2
Bone marrow (not usually needed)
Serum B12 level Normal
Red blood cell folate level Decreased
Folic acid deficiency

VITAMIN B_{12} DEFICIENCY (PERNICIOUS ANEMIA)

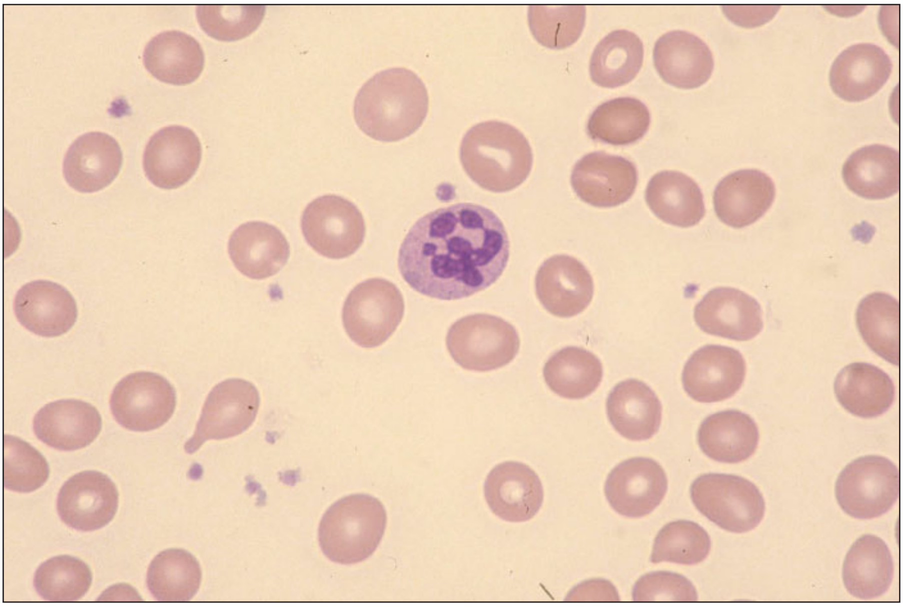


Figure IIA3-3

Peripheral blood smear.

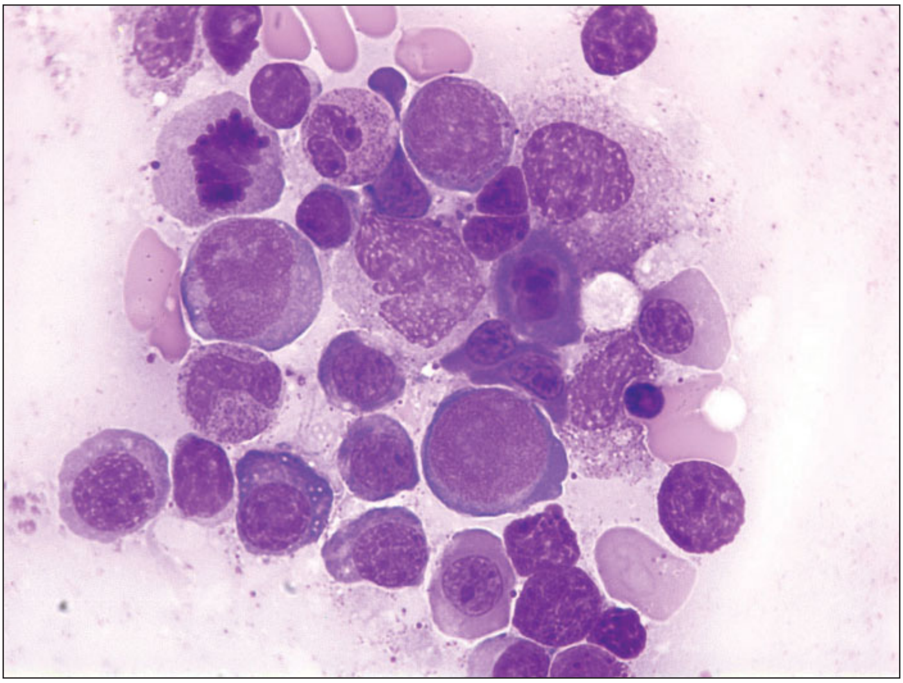


Figure IIA3-4

Bone marrow smear.

Clinical Features

- Usually occurs in persons older than 60 years
- Insidious onset
- Fatigue, weakness, yellowish waxy pallor
- Smooth tongue
- Gastrointestinal complaints
- Paresthesia, mental changes, spastic gait

Pathology

- Abnormal DNA synthesis
  - Ineffective hematopoiesis
- Causes
  - Dietary lack of vitamin B_{12} (rare in the United States)
  - Antibodies to intrinsic factor or antibodies to the parietal cell components
  - Decreased ileal absorption
  - Decreased availability (anatomic abnormalities)
  - Transcobalamin II deficiency
  - Cellular metabolic disorders (nitrous oxide)

Laboratory Features

White Blood Cells

- Neutropenia
- Hypersegmented neutrophils and eosinophils

Platelets

- Thrombocytopenia
- Large platelets present

Red Blood Cells

- Macrocytic, normochromic anemia
- Oval macrocytes
- Anisocytosis, poikilocytosis
- Nucleated red blood cells on peripheral smear
- Howell-Jolly bodies, basophilic stippling, Cabot rings
- Reticulocyte relative number normal but reticulocyte production index <2

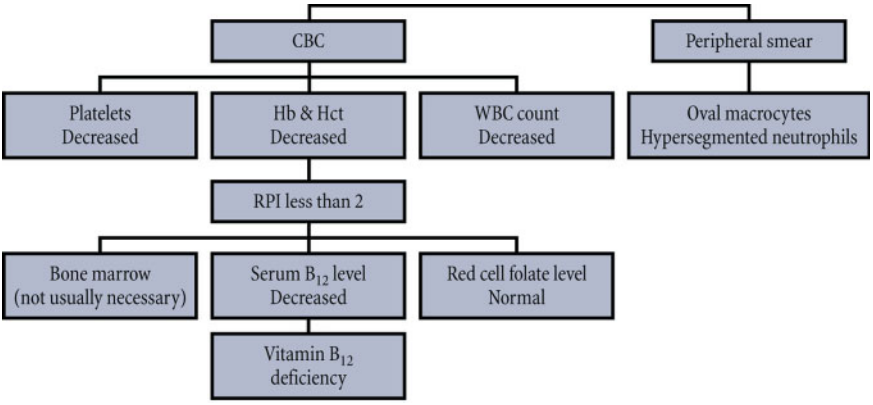
Bone Marrow

- Hypercellular, myeloid:erythroid ratio about 1:1
- Megaloblastic in erythroid granulocytic and megakaryocytic cell lines
- Giant metamyelocytes present

Chemistries

- Increased lactic dehydrogenase level
- Increased unconjugated bilirubin level
- Decreased haptoglobin level
- Increased iron level
- Decreased B_{12} levels

Diagnostic Scheme


CBC
Peripheral smear
Platelets Decreased
Hb & Hct Decreased
WBC count Decreased
Oval macrocytes Hypersegmented neutrophils
RPI less than 2
Bone marrow (not usually necessary)
Serum B_{12} level Decreased
Red cell folate level Normal
Vitamin B_{12} deficiency

CHAPTER 4

Hypoproliferative Anemias

ANEMIA CAUSED BY MYELOPHTHISIS

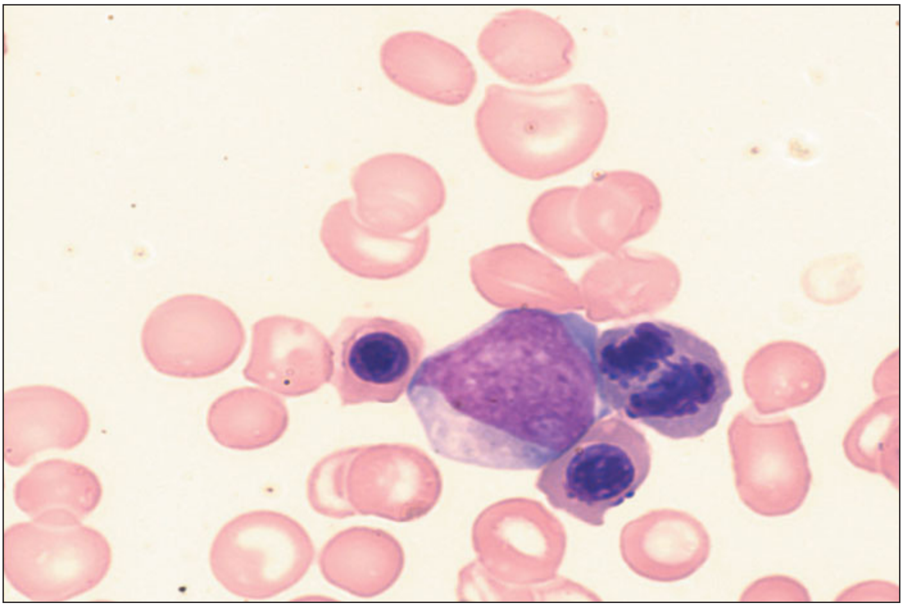


Figure IIA4-1

Peripheral blood smear.

Clinical Features

- Weakness, fatigue
- Hepatosplenomegaly
- Hypersplenism

Pathology

- Marrow invasion (myelophthisis)
  - Tumor
  - Primary myelofibrosis

Laboratory Features

White Blood Cells

- Variable
- Immature granulocytes seen on the peripheral smear

Platelets

- Occasional giant platelets
- Normal to decreased

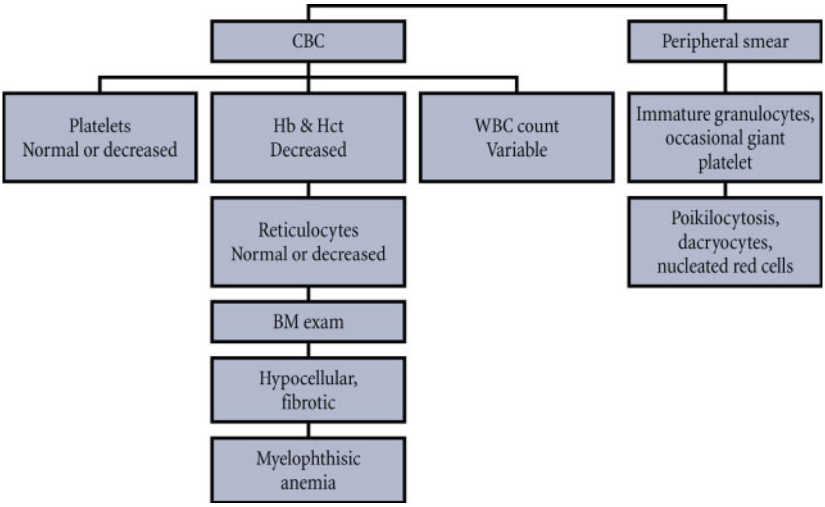
Red Blood Cells

- Normocytic, normochromic
- Poikilocytosis
- Dacryocytes
- Nucleated red blood cells seen on the peripheral smear

Bone Marrow

- Nonspecific changes or even normal morphology
- Bone marrow biopsy may reveal fibrosis

Diagnostic Scheme


CBC
Peripheral smear
Platelets Normal or decreased
Hb & Hct Decreased
WBC count Variable
Immature granulocytes, occasional giant platelet
Reticulocytes Normal or decreased
Poikilocytosis, dacryocytes, nucleated red cells
BM exam
Hypocellular, fibrotic
Myelophthisic anemia

ACQUIRED APLASTIC ANEMIA

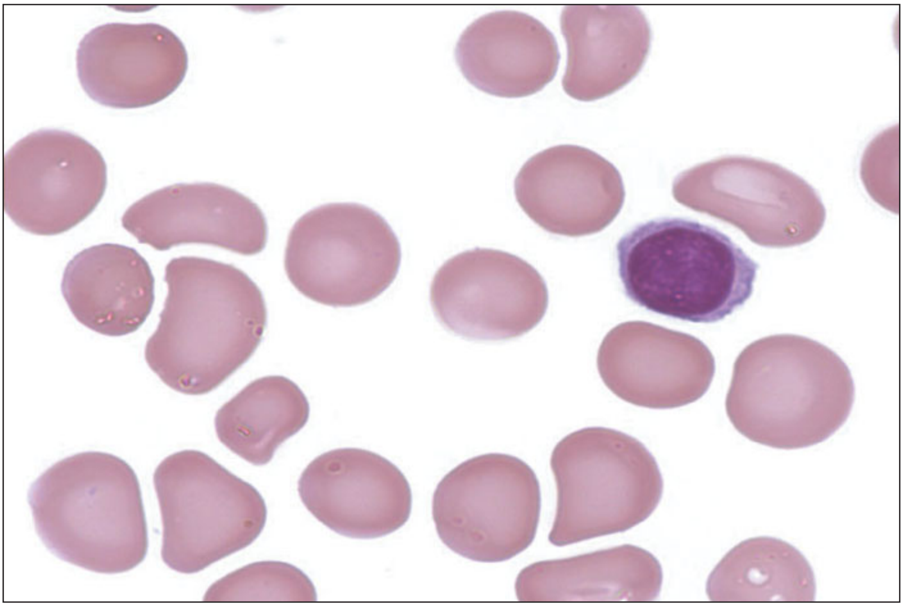


Figure **IIA4-2**

Peripheral blood smear.

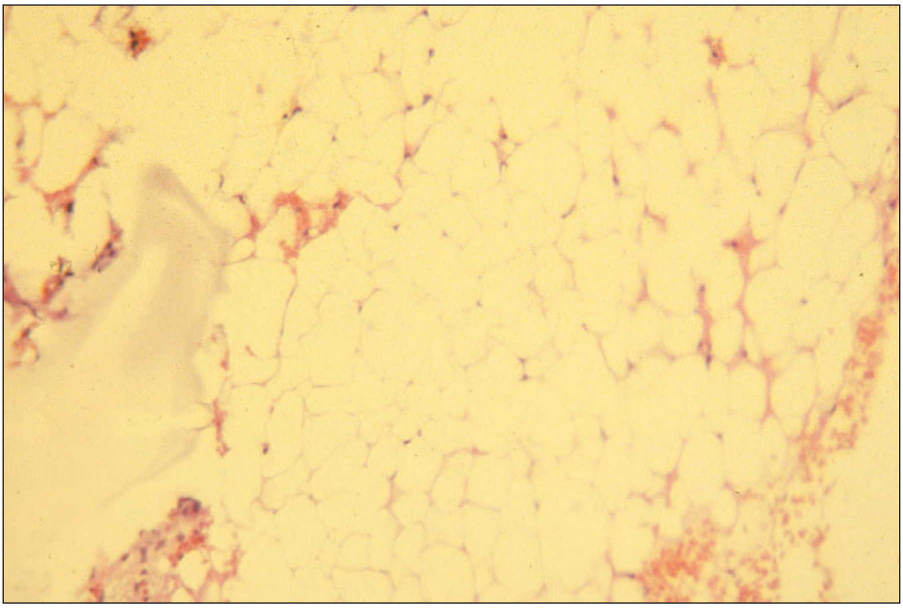


Figure **IIA4-3**

Bone marrow biopsy.

Clinical Features

- Weakness
- Dizziness
- Increased tendency for bruising
- Infections

Pathology

- Pancytopenia
  - Idiopathic
  - Chemical agents
  - Antimicrobials
  - Immunologic disorders
  - Radiation
  - Viral infections
- Decreased CD34 stem cells
- Paroxysmal nocturnal hemoglobinuria

Laboratory Features

White Blood Cells

- Decreased neutrophils
- Lymphocyte count is normal

Platelets

- Decreased

Red Blood Cells

- Normocytic, normochromic anemia but may be slightly macrocytic
- Red blood cell distribution width normal
- Corrected reticulocyte count decreased

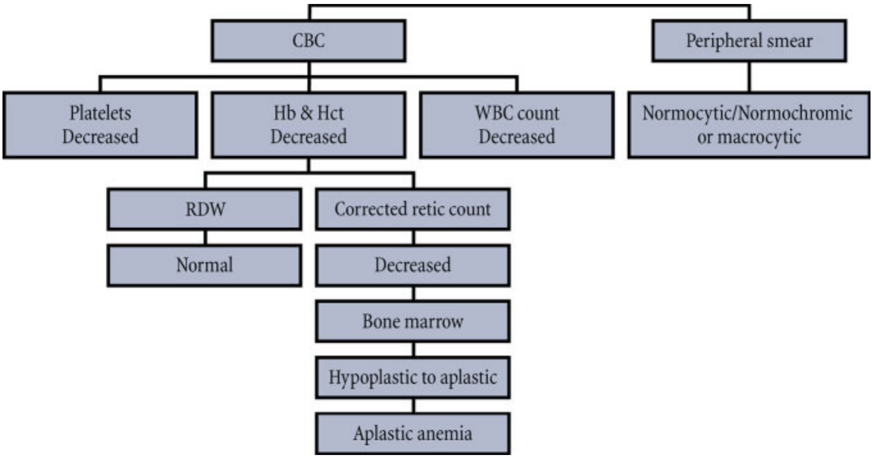
Bone Marrow

- Hypocellular

Criteria for the Diagnosis of Severe Aplastic Anemia

- Neutrophil count less than 0.5×10^9/L
- Platelet count $<20 \times 10^9$/L
- Corrected reticulocyte count <1% of red blood cells
- Bone marrow cellularity <30%
- No other pathology

Diagnostic Scheme


CBC
Peripheral smear
Platelets Decreased
Hb & Hct Decreased
WBC count Decreased
Normocytic/Normochromic or macrocytic
RDW
Corrected retic count
Normal
Decreased
Bone marrow
Hypoplastic to aplastic
Aplastic anemia

CONGENITAL DYSERYTHROPOIETIC ANEMIA

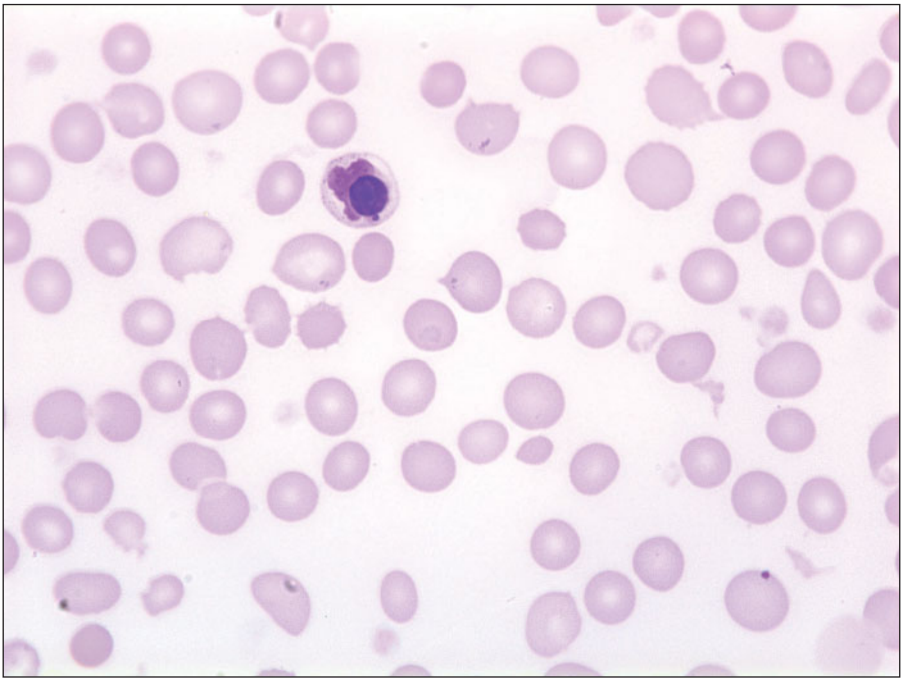


Figure IIA4-4

Peripheral blood smear.

Clinical Features

- Type I
    - Autosomal recessive inheritance
    - Male:female ratio 1.25:1
    - Icterus, splenomegaly, brown skin pigmentation, finger and toe abnormalities
- Type II
    - Autosomal recessive inheritance
    - Male:female ratio 1:1
    - Jaundice, hepatosplenomegaly, gallstones
- Type III
    - Autosomal dominance inheritance
    - Male:female ratio 1.9:1

Pathology

- Abnormal erythroid production
- Inherited marrow disorders
- Ineffective erythropoiesis because a discrepancy exists between erythroid output from marrow to circulation, resulting in anemia

Laboratory Features

Type I

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

Red Blood Cells

- Mild anemia
- Reticulocyte count 1–7% of red blood cells
- Mean corpuscular volume slightly increased
- Anisocytosis, poikilocytosis
- Basophilic stippling
- Acidified serum test result negative

Bone Marrow

- Erythroid hyperplasia
- Megaloblastic
- Chromatin bridging

Type II

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

Red Blood Cells

- Normocytic/normochromic anemia
- Anisocytosis, poikilocytosis
- Dacryocytes
- Basophilic stippling
- Cells lysed by 30% acidified sera from healthy persons but not by the patient's own serum
- Negative sugar water test result

Bone Marrow

- Gaucher-like cells
- Erythroid hyperplasia
- Normoblastic
- Binuclearity, multinuclearity

Type III

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

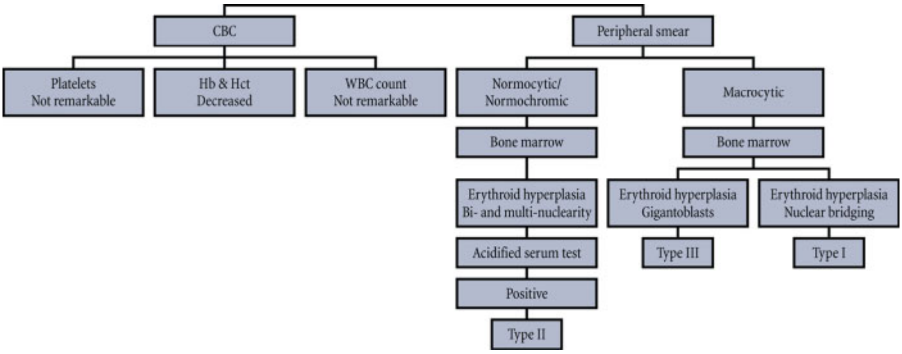
Red Blood Cells

- Mild to moderate anemia
- Mean corpuscular volume normal to slightly increased
- Negative acidified serum test result

Bone Marrow

- Erythroid hyperplasia
- Not megaloblastic
- Multinuclearity

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Decreased
WBC count Not remarkable
Normocytic/ Normochromic
Macrocytic
Bone marrow
Bone marrow
Erythroid hyperplasia Bi- and multi-nuclearity
Erythroid hyperplasia Gigantoblasts
Erythroid hyperplasia Nuclear bridging
Acidified serum test
Type III
Type I
Positive
Type II

CONGENITAL PURE RED BLOOD CELL APLASIA (DIAMOND-BLACKFAN ANEMIA)

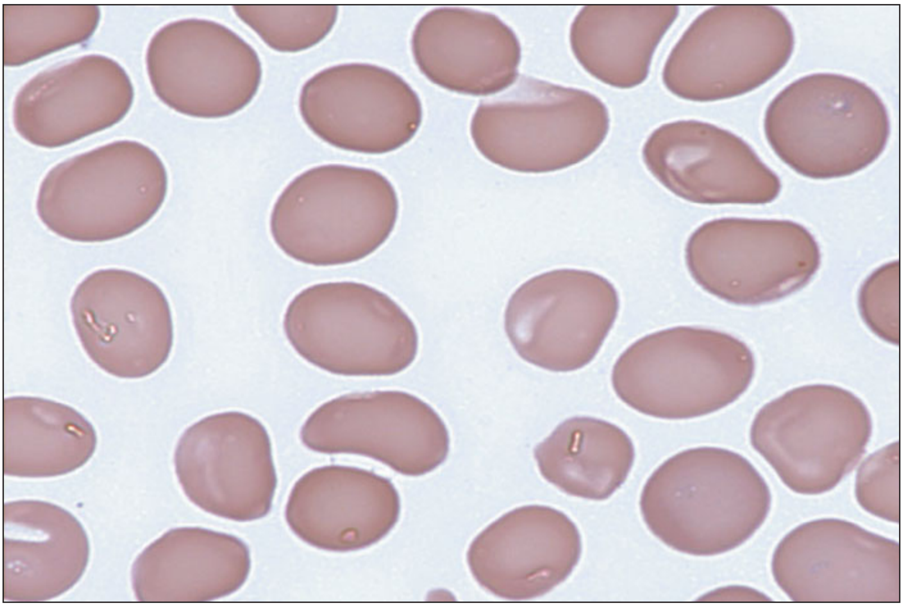


Figure IIA4-5

Peripheral blood smear.

Clinical Features

- Congenital anomalies of kidneys, eyes, skeleton, and heart
- Pallor, listlessness, poor appetite, and failure to thrive, which may progress to congestive heart failure with breathlessness
- Hepatosplenomegaly

Pathology

- Etiology basically unknown
- Intrinsic defect of erythroid precursors—may be a deficiency of adenosine deaminase and purine nucleoside phosphorylase
- The decreased purine nucleoside phosphorylase may result in the accumulation of toxic metabolites that inhibit cell replication
- Red blood cell precursors are not responsive to erythropoietin

Laboratory Features

White Blood Cells

- Normal to slightly decreased

Platelets

- Normal to slightly increased

Red Blood Cells

- Decreased
- Reticulocyte count decreased
- Erythropoietin increased

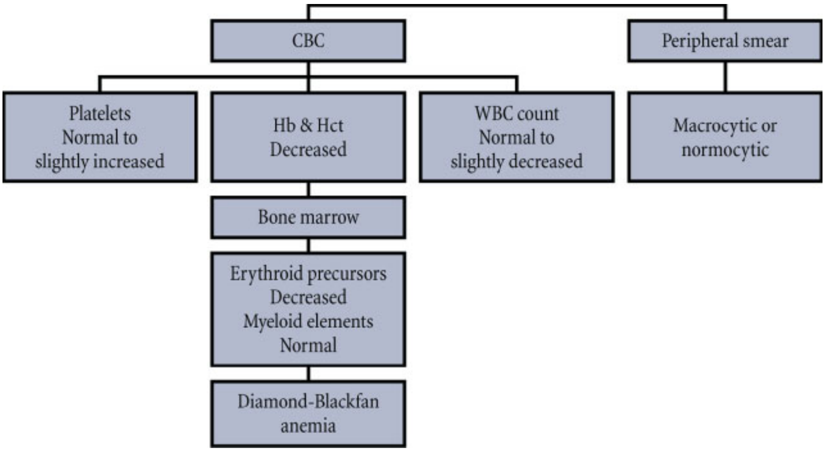
Bone Marrow

- Myeloid elements appear normal
- Erythroid precursors decreased with a predominance of pronormoblasts

Chemistries

- Serum iron level normal to slightly increased
- % iron saturation increased

Diagnostic Scheme


CBC
Peripheral smear
Platelets Normal to slightly increased
Hb & Hct Decreased
WBC count Normal to slightly decreased
Macrocytic or normocytic
Bone marrow
Erythroid precursors Decreased Myeloid elements Normal
Diamond-Blackfan anemia

FANCONI'S ANEMIA

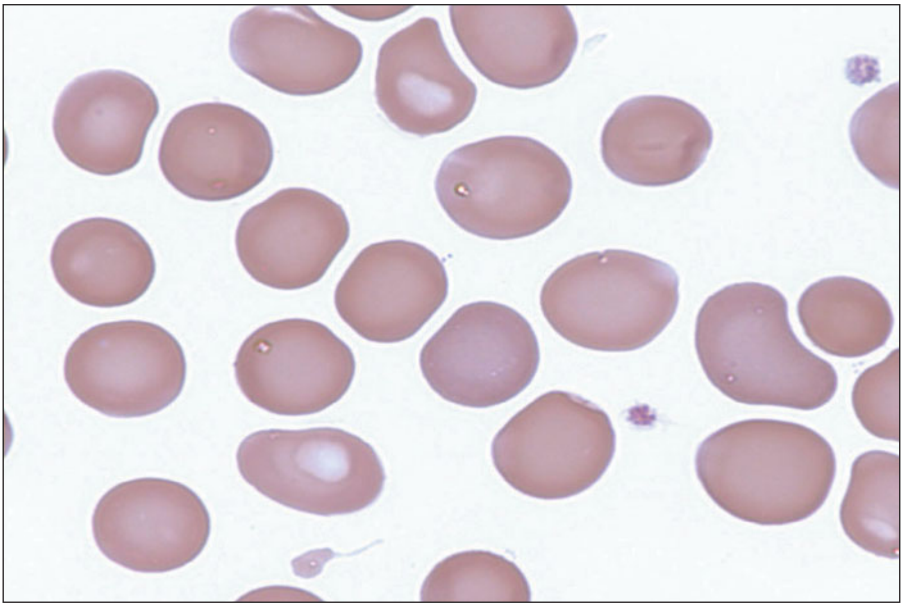


Figure IIA4-6

Peripheral blood smear.

Clinical Features

- Short stature
- Skin pigmentation
- Renal anomalies
- Bone dysplasia
- Microcephaly
- Mental retardation
- Infections
- Male:female ratio 1–3:1

Pathology

- Autosomal recessive inheritance
- Underlying defect is not entirely elucidated, may be a defect in DNA repair
- Chromosomal abnormalities include breaks, gaps, endoreplications, rearrangements, and exchanges

Laboratory Features

White Blood Cells

- Decreased granulocytes

Platelets

- Decreased

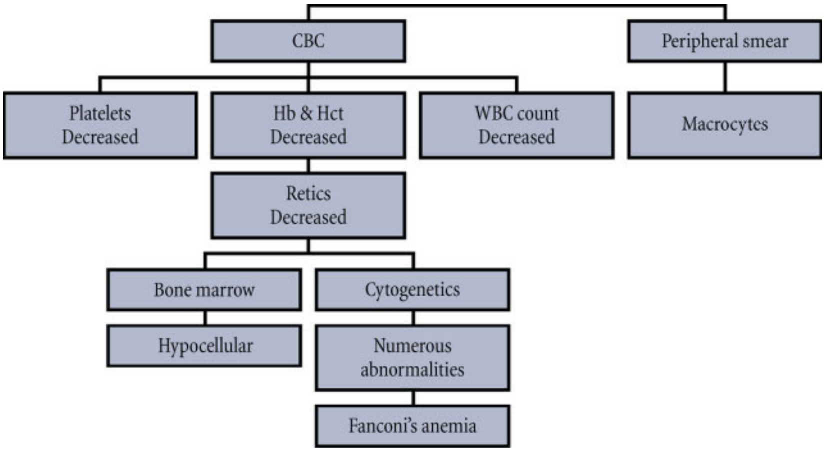
Red Blood Cells

- Macrocytic anemia
- Increased hemoglobin F

Bone Marrow

- Hypocellular
- Possible dyserythropoiesis

Diagnostic Scheme


CBC
Peripheral smear
Platelets Decreased
Hb & Hct Decreased
WBC count Decreased
Macrocytes
Retics Decreased
Bone marrow
Cytogenetics
Hypocellular
Numerous abnormalities
Fanconi's anemia

PURE RED CELL APLASIA

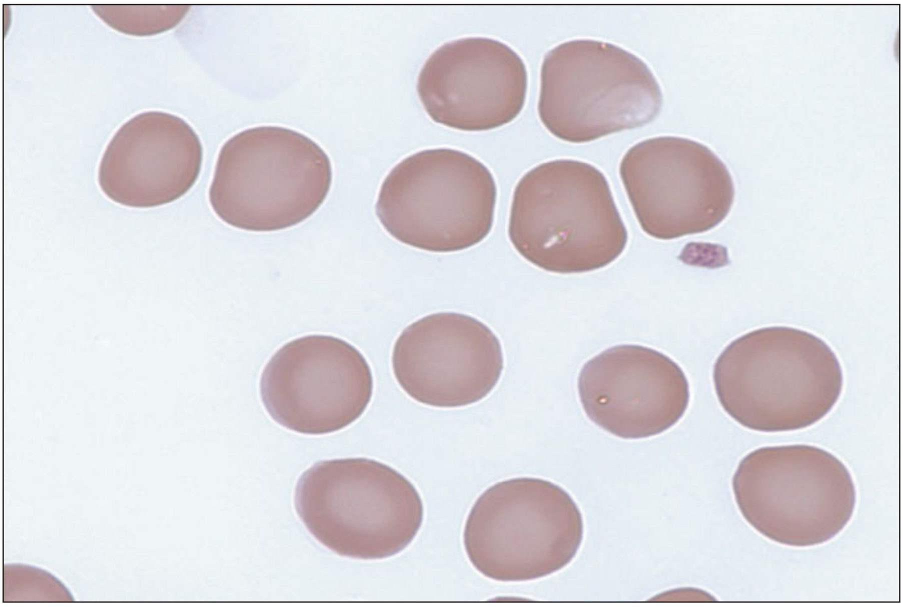


Figure IIA4-7

Peripheral blood smear.

Clinical Features

- Severe anemia—weakness, headache, vertigo, fatigue, tinnitus, and irritability
- Primary
  - Idiopathic
  - Immune mediated
- Secondary
  - Associated with thymoma
  - Neoplasia
  - Drugs
  - Infections

Pathology

- Erythropoiesis inhibited primarily by immune mechanism
- T cells, particularly large granular lymphocytes, may be involved in the suppression of erythropoiesis
- Specific attachment on erythroid precursors by the parvovirus B-19
- Clonal abnormality as a prodrome to myelodysplastic syndrome

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

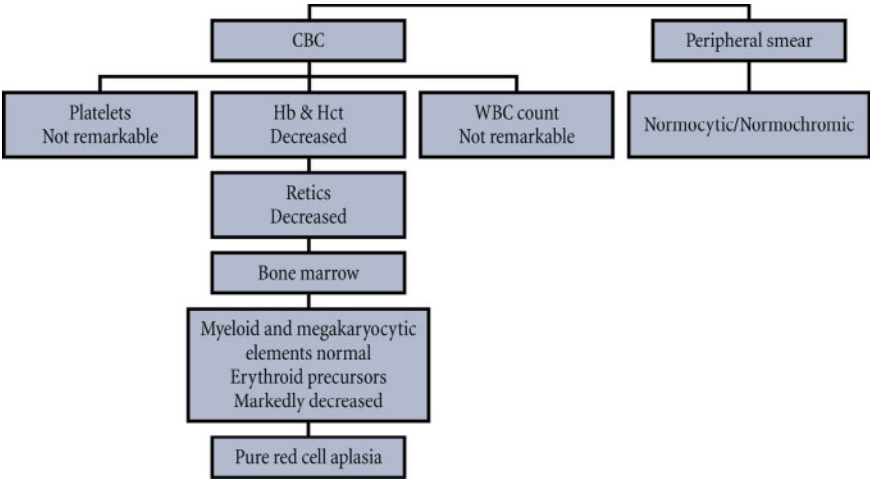
Red Blood Cells

- Normocytic/normochromic anemia
- Hemoglobin level decreased
- Hematocrit level decreased
- Reticulocytes absent

Bone Marrow

- Absence of erythroid cells
- Myeloid and megakaryocytic elements are preserved

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Decreased
WBC count Not remarkable
Normocytic/Normochromic
Retics Decreased
Bone marrow
Myeloid and megakaryocytic elements normal Erythroid precursors Markedly decreased
Pure red cell aplasia

CHAPTER 5

Hemoglobinopathies

α THALASSEMIA (4 GENE DELETION)

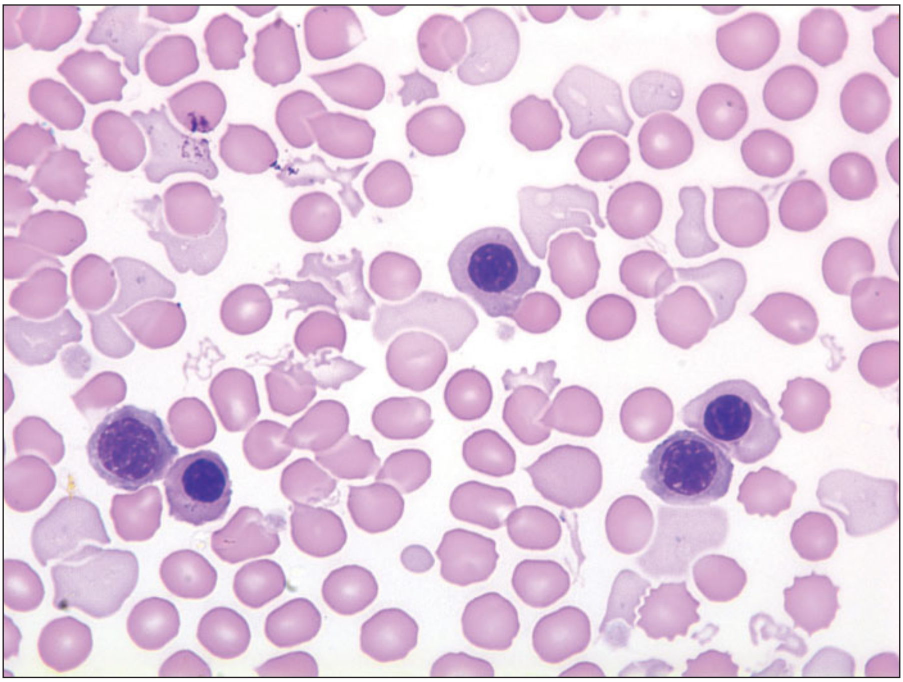


Figure IIA5-1

Cord blood smear.

Clinical Features

- Produces hydrops fetalis, and affected infants are either stillborn or die within hours of birth
- Marked hepatosplenomegaly
- Marked anemia

Pathology

- Parents are usually heterozygous for α thalassemia (– –/αα)
- No α chains are produced (– –/– –)
- Free γ chains form tetrads, producing hemoglobin
- Bart's hemoglobin
- Excess β chains form tetramers and inclusions in red blood cells, which shortens survival

Laboratory Features

White Blood Cells

- Not remarkable

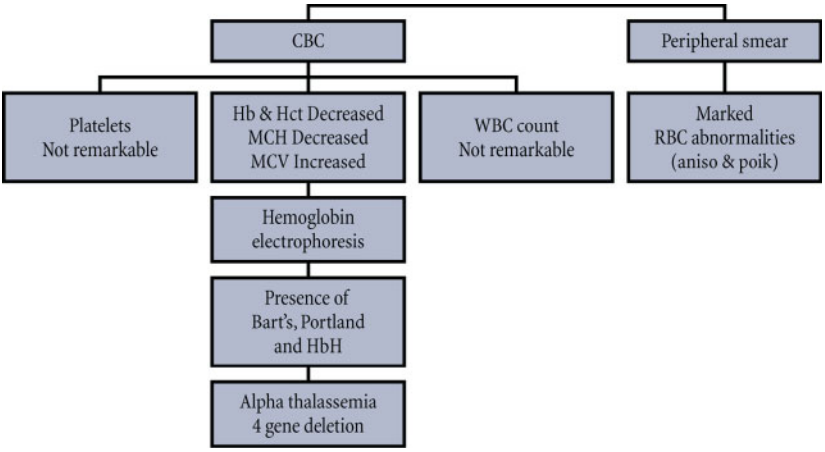
Platelets

- Not remarkable

Red Blood Cells

- Macrocytic/hypochromic anemia
- Mean corpuscular hemoglobin level decreased
- Mean corpuscular volume increased
- Increased nucleated red blood cells
- 80–90% Bart's hemoglobin
- 10–20% Portland hemoglobin
- Trace of hemoglobin H

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Decreased MCH Decreased MCV Increased
WBC count Not remarkable
Marked RBC abnormalities (aniso & poik)
Hemoglobin electrophoresis
Presence of Bart's, Portland and HbH
Alpha thalassemia 4 gene deletion

α THALASSEMIA (3 GENE DELETION—HEMOGLOBIN H DISEASE)

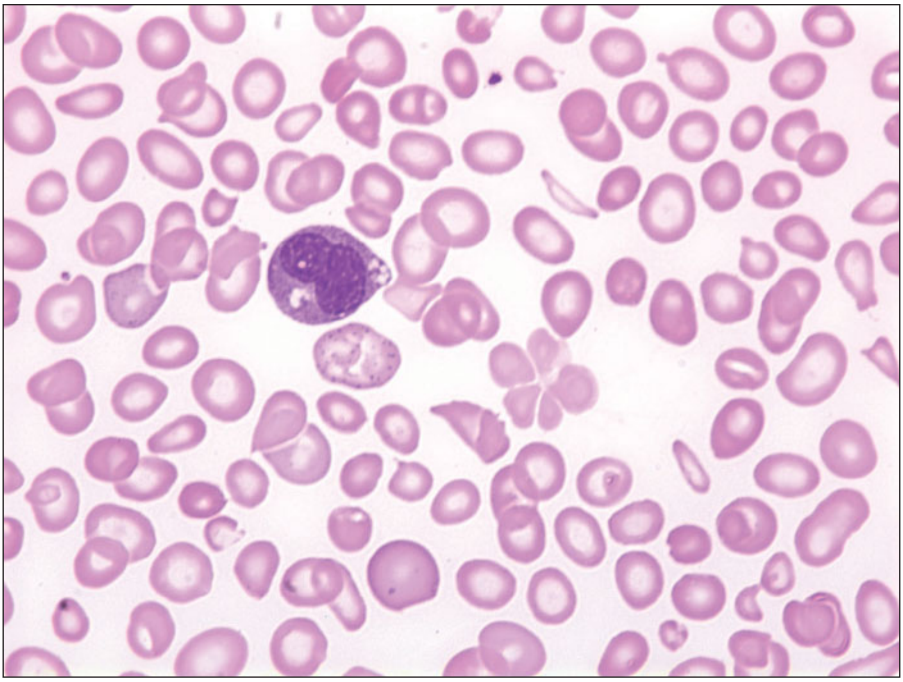


Figure IIA5-2

Peripheral blood smear.

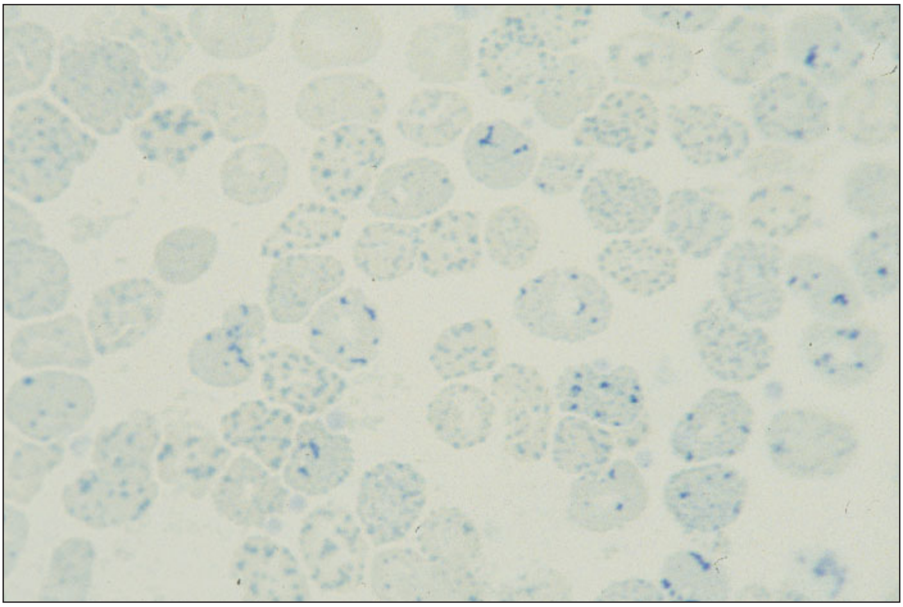


Figure IIA5-3

Brilliant cresyl blue stain.

Clinical Features

- Splenomegaly
- Variable anemia, more severe during pregnancy, infections, and exposure to oxidant drugs

Pathology

- Deletion of three α genes ($--/-\alpha$)
  - Reduced hemoglobin A and thus oxygen delivery
- Excess unpaired β chains are present and form unstable tetramers (β_4) (hemoglobin H)
  - Hemoglobin H has high oxygen affinity, resulting in decreased oxygen delivery
- Tetramers can cause disturbances in red blood cell metabolism, membrane function, and deformability, resulting in chronic hemolytic anemia

Laboratory Features

White Blood Cells

- Not remarkable

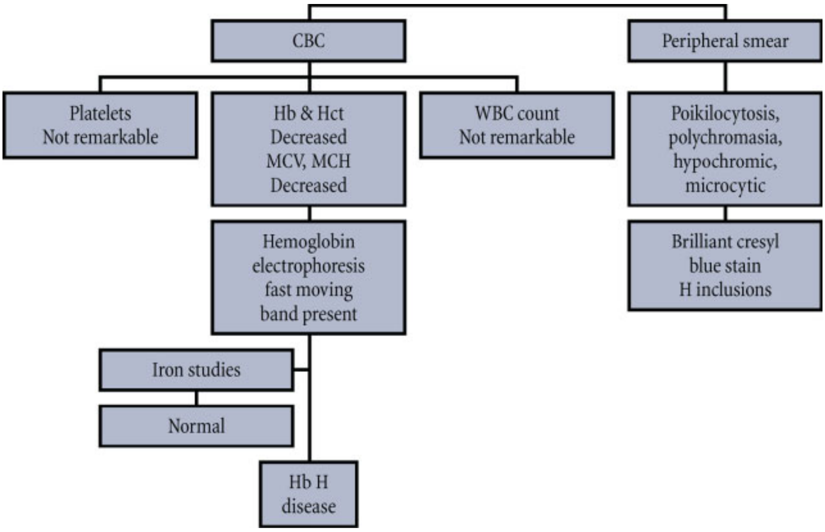
Platelets

- Not remarkable

Red Blood Cells

- Hemoglobin level, 8.0–10.0 g/dL
- Reticulocyte count, 5–10% of red blood cells
- Microcytic/hypochromic anemia
- Increased red blood cell distribution width
- Poikilocytosis
- Polychromasia

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Decreased MCV, MCH Decreased
WBC count Not remarkable
Poikilocytosis, polychromasia, hypochromic, microcytic
Hemoglobin electrophoresis fast moving band present
Brilliant cresyl blue stain H inclusions
Iron studies
Normal
Hb H disease

α THALASSEMIA MINOR AND SILENT CARRIER

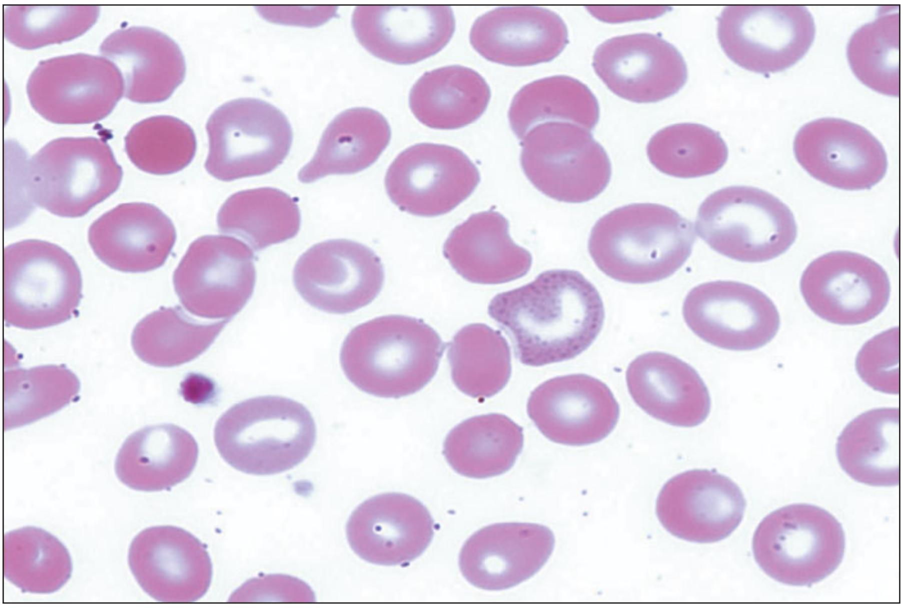


Figure **IIA5-4**

Peripheral blood smear.

Clinical Features

- No clinical disease is seen with either the trait or the silent carrier

Pathology

Minor or Trait

- Decreased production of α-globin chains
- Exists in two forms:
  - Heterozygous α^0 thalassemia ($--/\alpha\alpha$)
  - Homozygous α^+ thalassemia ($-\alpha/-\alpha$)
- Both forms are common in Southeast Asians, Chinese, and Filipinos
- Homozygous form is common in African Americans (about 3%)

Silent Carrier

- Heterozygous α^+ ($-\alpha/\alpha\alpha$) is common in Southeast Asians, Chinese, and Filipinos
- About 28% of African Americans have the heterozygous α^+ thalassemia

Laboratory Features

Minor or Trait

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

Red Blood Cells

- Microcytic and slightly hypochromic anemia
- Poikilocytosis
- Codocytes
- Normal or slightly increased red blood cell distribution width
- Hemoglobin H inclusions may occasionally be found in brilliant cresyl blue (BCB) prep
- 5–15% Bart's hemoglobin in cord blood (normal after about age 3 months)

Silent Carrier

White Blood Cells

- Not remarkable

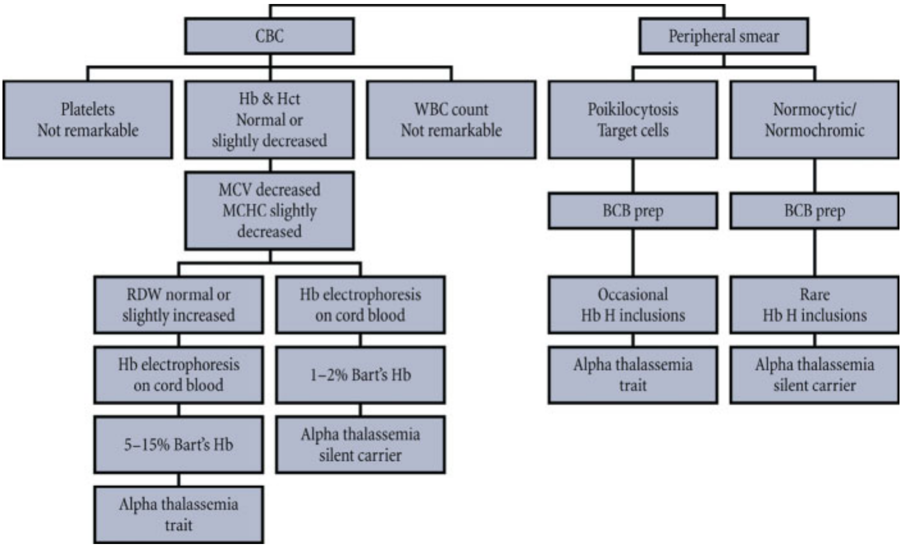
Platelets

- Not remarkable

Red Blood Cells

- No hematologic manifestations
- 1–2% Bart's hemoglobin found at birth
- Rare hemoglobin H inclusion found in BCB prep

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Normal or slightly decreased
WBC count Not remarkable
Poikilocytosis Target cells
Normocytic/ Normochromic
MCV decreased MCHC slightly decreased
BCB prep
BCB prep
RDW normal or slightly increased
Hb electrophoresis on cord blood
Occasional Hb H inclusions
Rare Hb H inclusions
Hb electrophoresis on cord blood
1–2% Bart's Hb
Alpha thalassemia trait
Alpha thalassemia silent carrier
5–15% Bart's Hb
Alpha thalassemia silent carrier
Alpha thalassemia trait

β THALASSEMIA

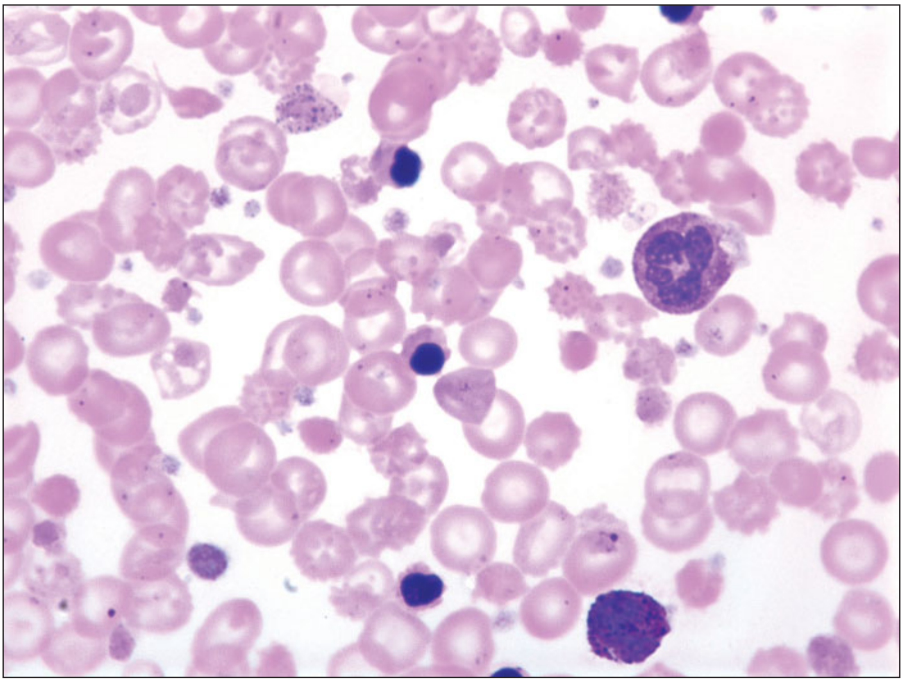


Figure **IIA5-5**

Peripheral blood smear—major.

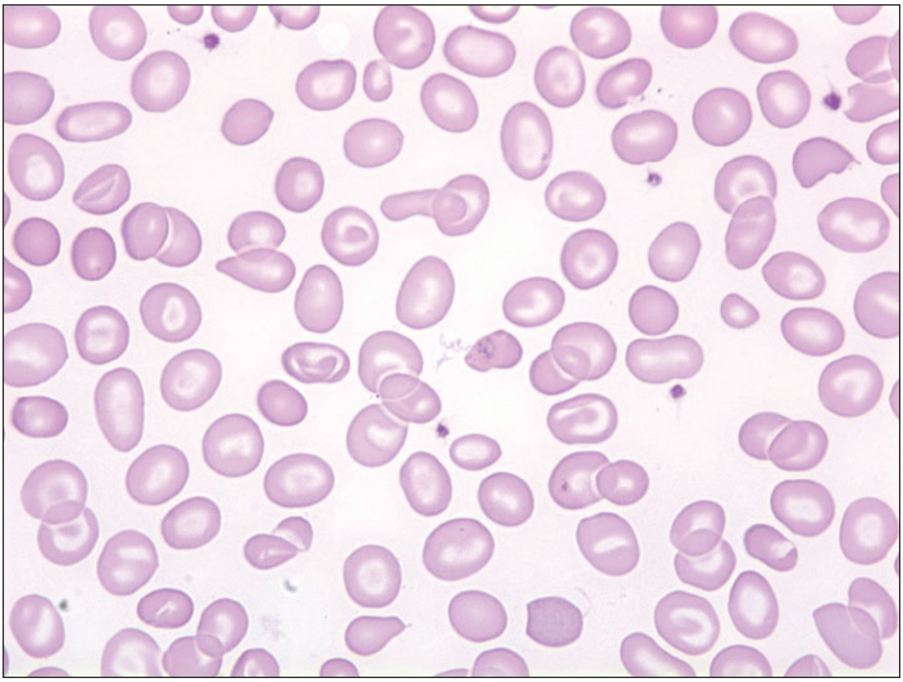


Figure **IIA5-6**

Peripheral blood smear—intermedia.

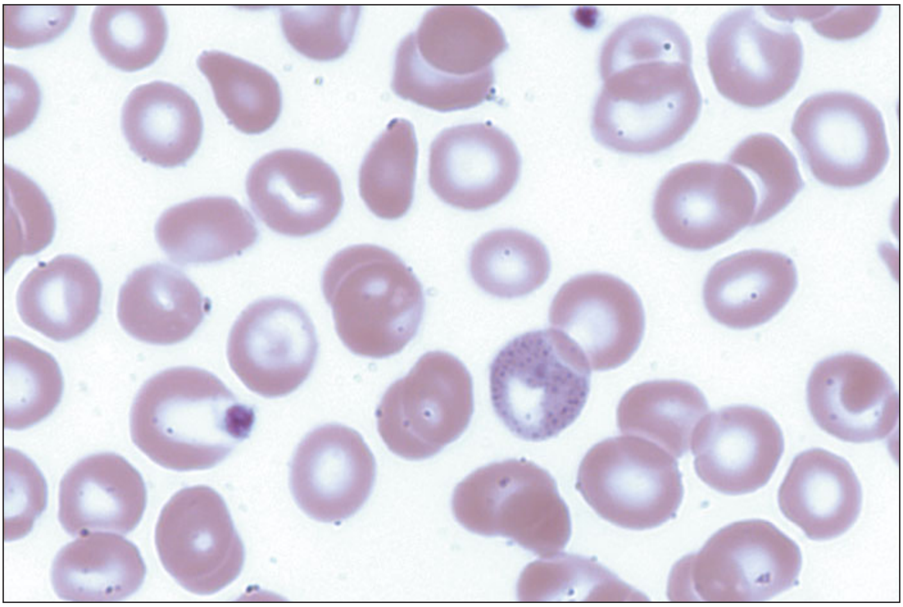


Figure **IIA5-7**

Peripheral blood smear—minor.

Clinical Features

- Major variant
  - Severe anemia
  - Transfusion dependent
  - Growth retardation
  - Massive hepatosplenomegaly
  - Severe ineffective erythropoiesis
  - Early death with iron overload
- Intermedia variant
  - Moderate anemia
  - Splenomegaly
  - Moderate, ineffective erythropoiesis
- Minor variant
  - Mild anemia
  - Usually no symptoms

Pathology

- β chain production is absent or diminished—the more β chain produced, the less severe the disease
- Unmatched α chains accumulate and aggregate
  - Ineffective erythropoiesis
  - Chronic hemolytic process
- Decreased erythrocyte hemoglobin production

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

Red Blood Cells

- Nucleated red blood cells on peripheral smear (found in major and intermedia)
- Hypochromic/microcytic anemia
- Target cells present
- Distorted cells
- Basophilic stippling
- Normal to increased red blood cell distribution width
- Increased red blood cell count relative to hemoglobin and hematocrit

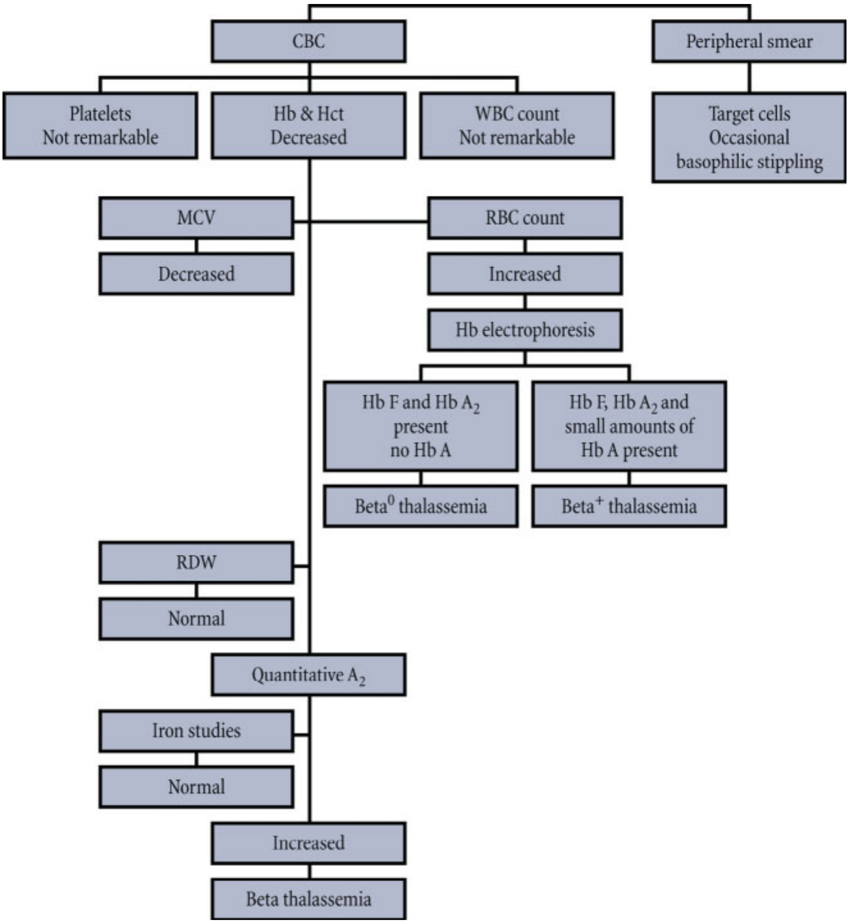
Bone Marrow

- Ineffective erythropoiesis because of the accumulation of α-globulin chains
- Extremely hyperplastic

Hemoglobin Electrophoresis

- Only hemoglobin F and hemoglobin A_2 are found in β^0 thalassemia
- Small amounts of hemoglobin A may be found in β^+ thalassemia
- Increased hemoglobin A_2 is indicative of β thalassemia

Diagnostic Scheme


CBC
Peripheral smear
Platelets
Not remarkable
Hb & Hct
Decreased
WBC count
Not remarkable
Target cells
Occasional
basophilic stippling
MCV
Decreased
RBC count
Increased
Hb electrophoresis
Hb F and Hb A_2
present
no Hb A
Hb F, Hb A_2 and
small amounts of
Hb A present
Beta^0 thalassemia
Beta$^+$ thalassemia
RDW
Normal
Quantitative A_2
Iron studies
Normal
Increased
Beta thalassemia

HEMOGLOBIN C

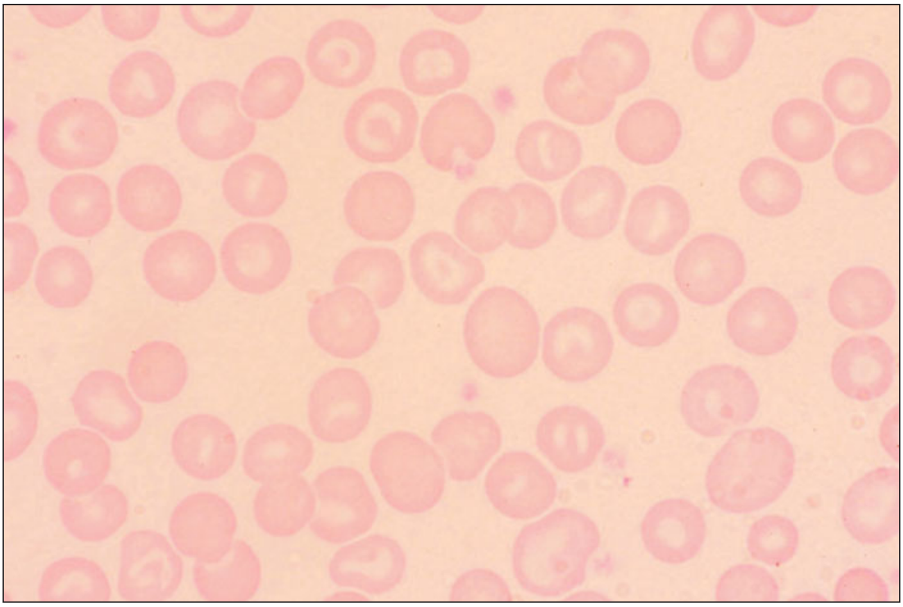


Figure IIA5-8

Peripheral blood smear—heterozygous.

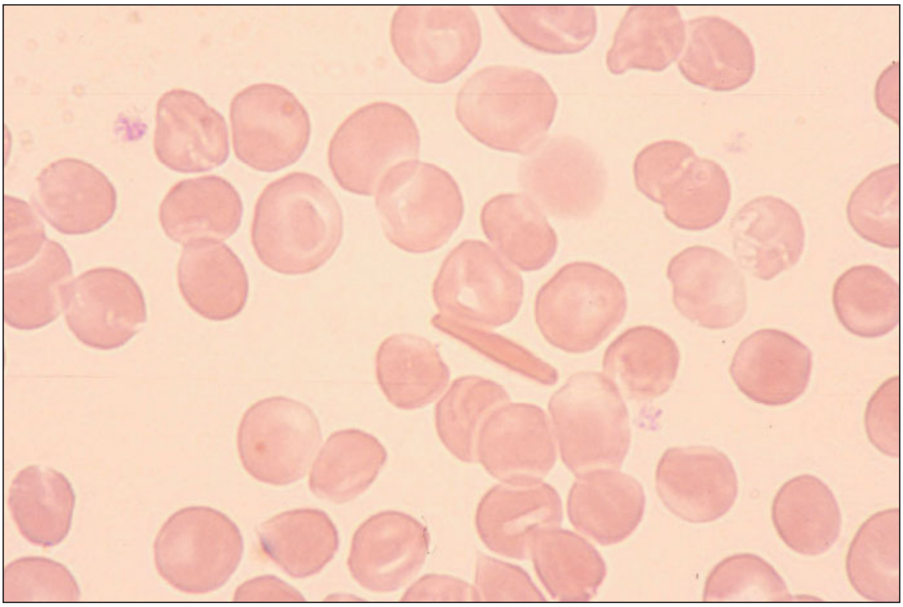


Figure IIA5-9

Peripheral blood smear—homozygous.

Clinical Features

- Mild to moderate hemolysis
- Palpable splenomegaly
- Cholelithiasis and aplastic crises may occur
- Arthralgia is common
- May be abdominal pain
- Hemoglobin C trait has no clinical manifestations

Pathology

- α_2/β_2 (glutamic acid replaced by lysine on amino acid 6)
- Relative insolubility of hemoglobin C causes red blood cells to become rigid
- Loss of potassium and cell hydration
- Cell is subject to fragmentation and loss of membrane material, resulting in microspherocytes

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

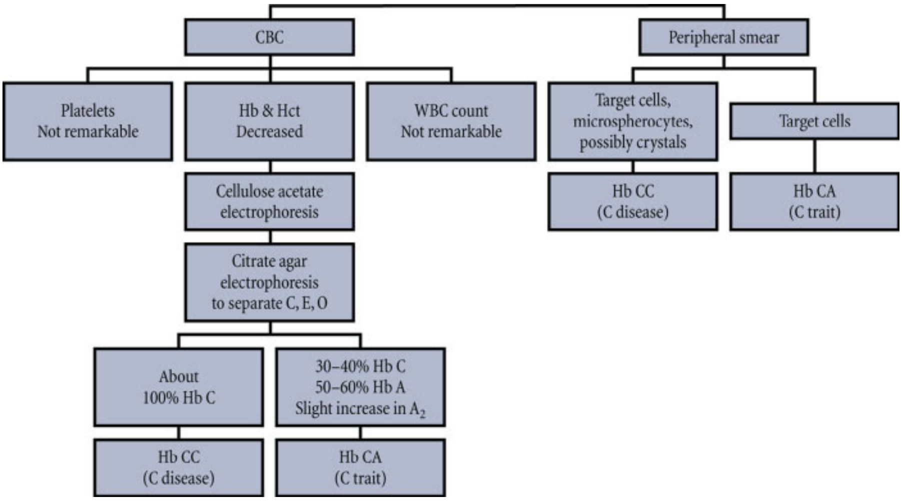
Red Blood Cells

- Microspherocytes present
- Reticulocyte count 4–8%
- Hematocrit level approximately 0.25-0.37 L/L
- Approximately 30–100% target cells
- C crystals seen in oxyhemoglobin state

Hemoglobin Electrophoresis

- Homozygous: about 100% hemoglobin C
- Heterozygous: 30–40% C, 50–60% A, slight increase in A_2

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Decreased
WBC count Not remarkable
Target cells, microspherocytes, possibly crystals
Target cells
Cellulose acetate electrophoresis
Hb CC (C disease)
Hb CA (C trait)
Citrate agar electrophoresis to separate C, E, O
About 100% Hb C
30–40% Hb C
50–60% Hb A
Slight increase in A2
Hb CC (C disease)
Hb CA (C trait)

HEMOGLOBIN CONSTANT SPRING SYNDROME

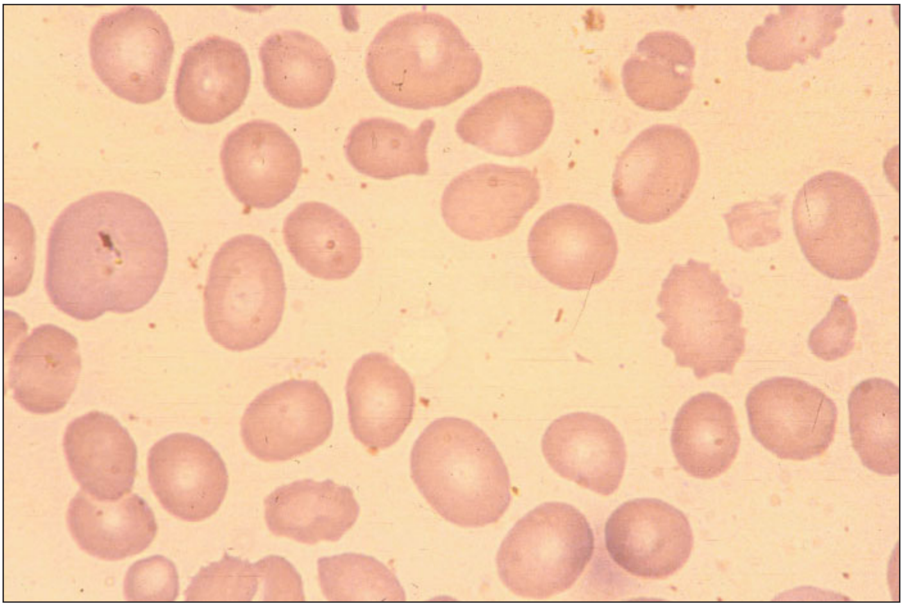


Figure IIA5-10

Peripheral blood smear.

Clinical Features

- Homozygotes have a condition similar to mild α thalassemia—mild anemia, mild jaundice, splenomegaly
- Heterozygotes usually have no clinical abnormalities
- Common in Thailand, Chinese, and Greek ancestry with α thalassemia syndromes
- May occur in about 40% of hemoglobin H disease in Southeast Asians

Pathology

- Four different types of hemoglobins
- Hemoglobin Constant Spring is formed from the combination of two structurally abnormal α chains, each elongated by 31 amino acids at the C-terminal end and two normal β chains
- The abnormal α chains are inefficiently synthesized owing to reduced stability of the messenger RNA translation apparatus
- The deficiency of α chain synthesis produces an α thalassemia–like syndrome

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

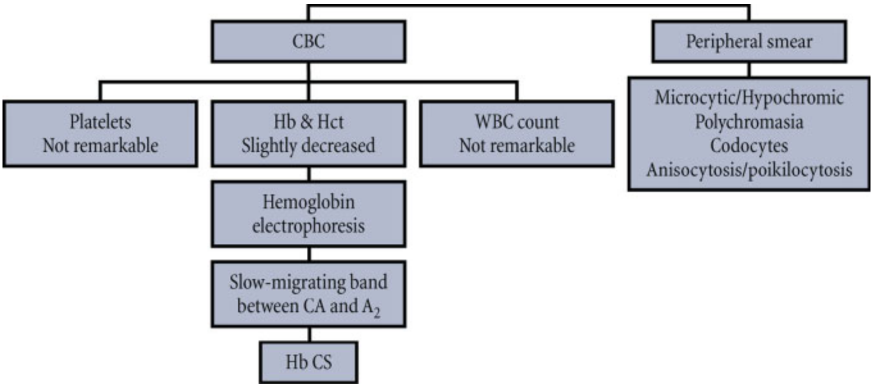
Red Blood Cells

- Mild microcytic, hypochromic anemia
- Hemoglobin level usually 9.0–11.0 g/dL
- Reticulocyte count, 3.5–7.5%
- Anisocytosis, poikilocytosis
- Codocytes

Hemoglobin Electrophoresis (Cellulose Acetate, pH 8.4)

- Migrates on the cathode side of hemoglobin A_2
- In homozygotes
  - Bart's hemoglobin present at birth
  - Hemoglobin Constant Spring 5–7%
  - Hemoglobins A_2 and F normal
- In heterozygotes
  - Hemoglobin Constant Spring 0.2–1.7%

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Slightly decreased
WBC count Not remarkable
Microcytic/Hypochromic Polychromasia Codocytes Anisocytosis/poikilocytosis
Hemoglobin electrophoresis
Slow-migrating band between CA and A2
Hb CS

HEMOGLOBIN D

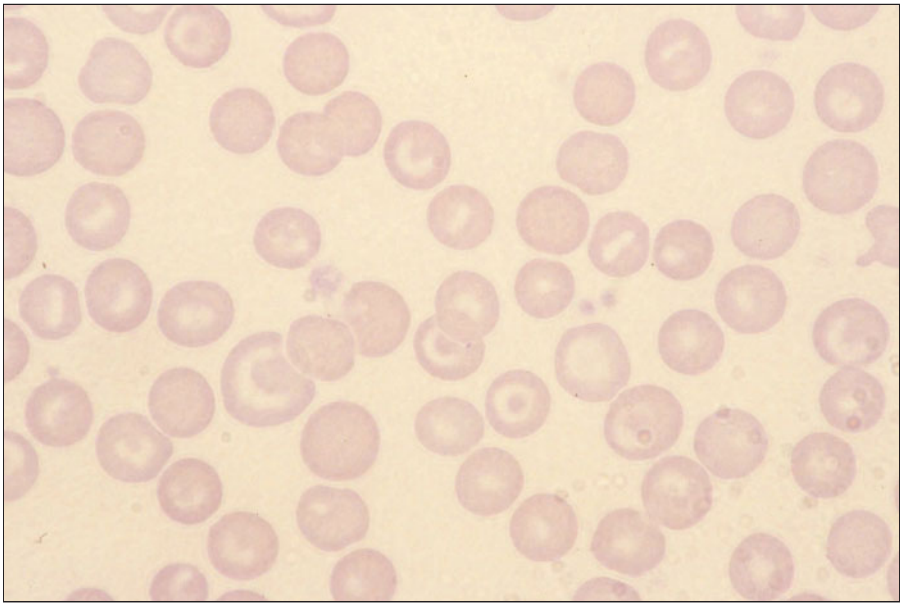


Figure IIA5-11

Peripheral blood smear.

Clinical Features

- Disorder is rare
- Homozygous individuals may have a mild anemia
- Both homozygous and heterozygous individuals are asymptomatic

Pathology

- α/β_2 (glutamic acid replaced by glycine on amino acid 121)
- Many variants are found
  - Hemoglobin D-Punjab and hemoglobin D Los Angeles are the most commonly encountered of the D hemoglobins in American Blacks (0.02%)

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

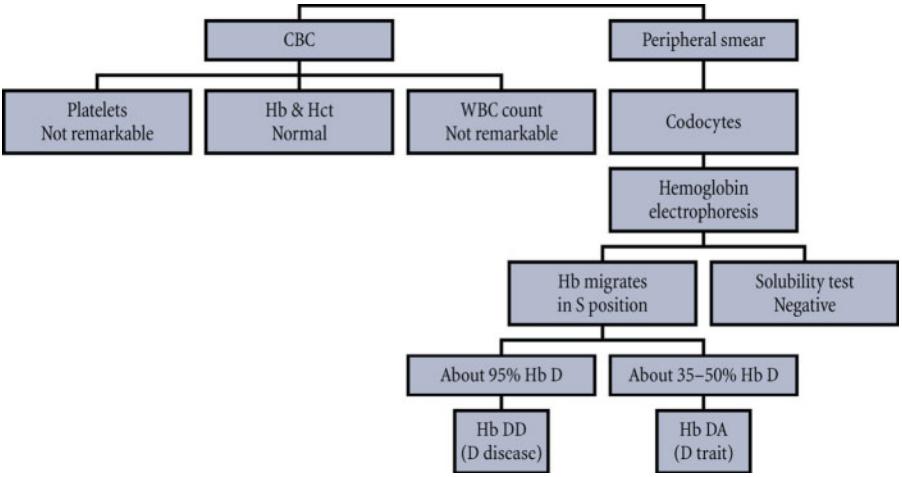
Red Blood Cells

- Homozygotes may have a normal hemoglobin level and no evidence of hemolysis
- Indices normal
- May see target cells
- May see decreased osmotic fragility

Hemoglobin Electrophoresis

- Homozygous
  - 95% D and normal A_2
  - Hemoglobin D migrates with S at pH 8.6 but does not sickle
  - Hemoglobin D migrates with A on acid electrophoresis

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Normal
WBC count Not remarkable
Codocytes
Hemoglobin electrophoresis
Hb migrates in S position
Solubility test Negative
About 95% Hb D
About 35–50% Hb D
Hb DD (D disease)
Hb DA (D trait)

HEMOGLOBIN E

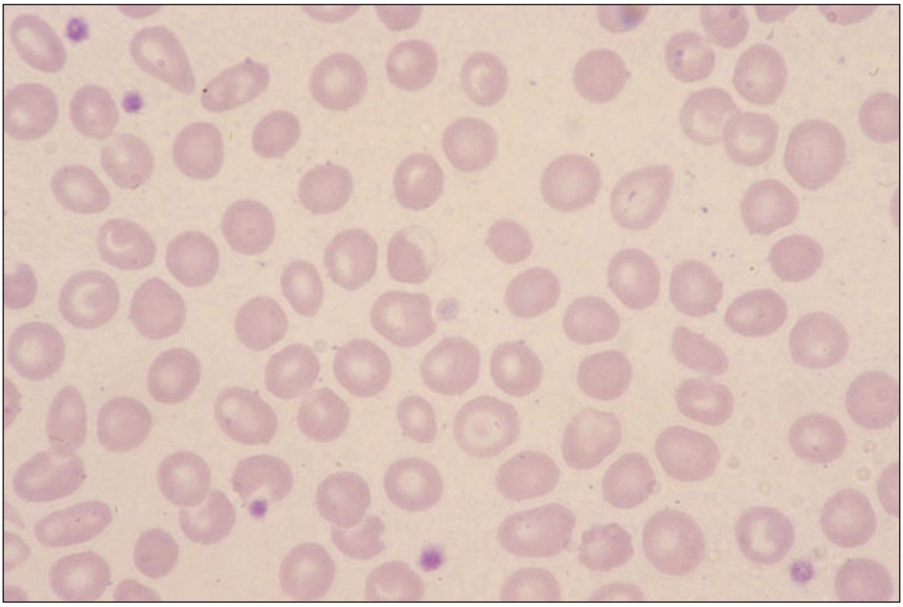


Figure IIA5-12

Peripheral blood smear.

Clinical Features

- Homozygous: mild or asymptomatic, microcytic anemia with decreased erythrocyte survival
- Heterozygous: symptomless, microcytosis

Pathology

- Substitution of lysine for glutamic acid in the β chain
- Hemoglobin is slightly unstable with oxidant stress
- Oxygen dissociation curve is shifted to the right, indicating that hemoglobin E has decreased oxygen affinity

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

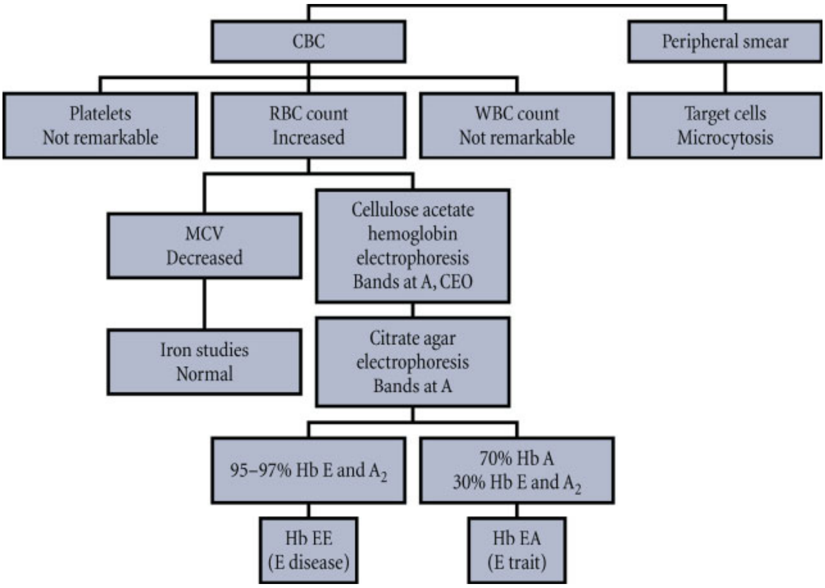
Red Blood Cells

- Hemoglobin level is 12.0–13.0 g/dL
- Decreased mean corpuscular volume
- Target cells present
- Increased red blood cells
- Normal or decreased reticulocyte count

Hemoglobin Electrophoresis

- Presence of hemoglobin E

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
RBC count Increased
WBC count Not remarkable
Target cells Microcytosis
MCV Decreased
Cellulose acetate hemoglobin electrophoresis Bands at A, CEO
Iron studies Normal
Citrate agar electrophoresis Bands at A
95–97% Hb E and A_2
70% Hb A 30% Hb E and A_2
Hb EE (E disease)
Hb EA (E trait)

HEMOGLOBIN E/β THALASSEMIA

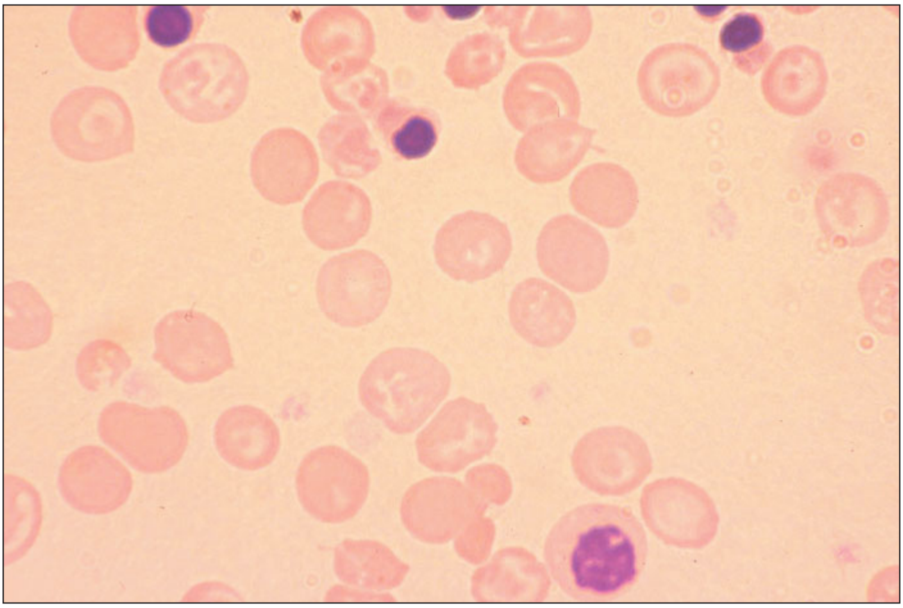


Figure IIA5-13

Peripheral blood smear.

Clinical Features

- Moderate to severe anemia
- The most severe type is E/β^0
- Anemia is generally more severe than in patients with hemoglobin S/β
- Anemia is more severe than in E trait
- Splenomegaly

Pathology

- This is the most common combination in Southeast Asians
- Double heterozygous for hemoglobin E and β thalassemia

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

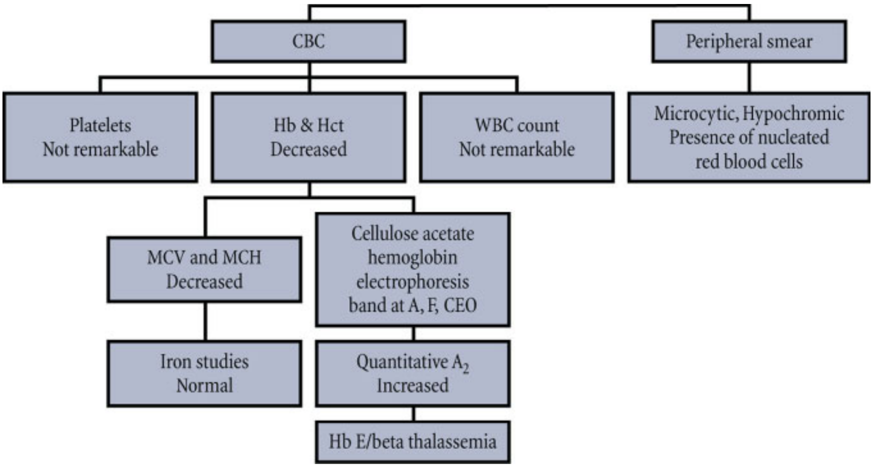
Red Blood Cells

- Decreased hemoglobin and hematocrit levels
- Microcytic, hypochromic anemia
- Presence of nucleated red blood cells

Hemoglobin Electrophoresis (Cellulose Acetate, pH 8.4)

- Bands at A, F, CEO

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Decreased
WBC count Not remarkable
Microcytic, Hypochromic Presence of nucleated red blood cells
MCV and MCH Decreased
Cellulose acetate hemoglobin electrophoresis band at A, F, CEO
Iron studies Normal
Quantitative A2 Increased
Hb E/beta thalassemia

HEMOGLOBIN LEPORE SYNDROME

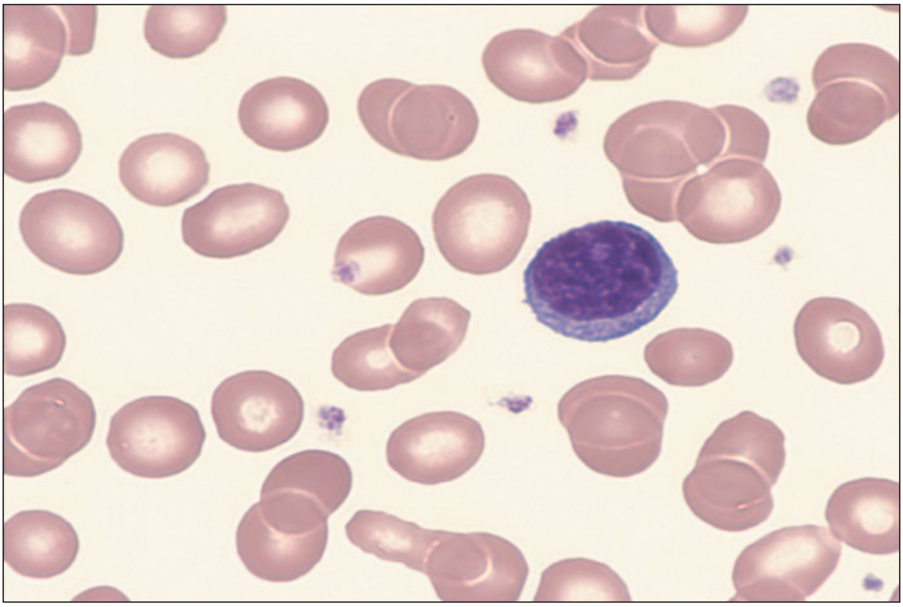


Figure IIA5-14

Peripheral blood smear—heterozygous.

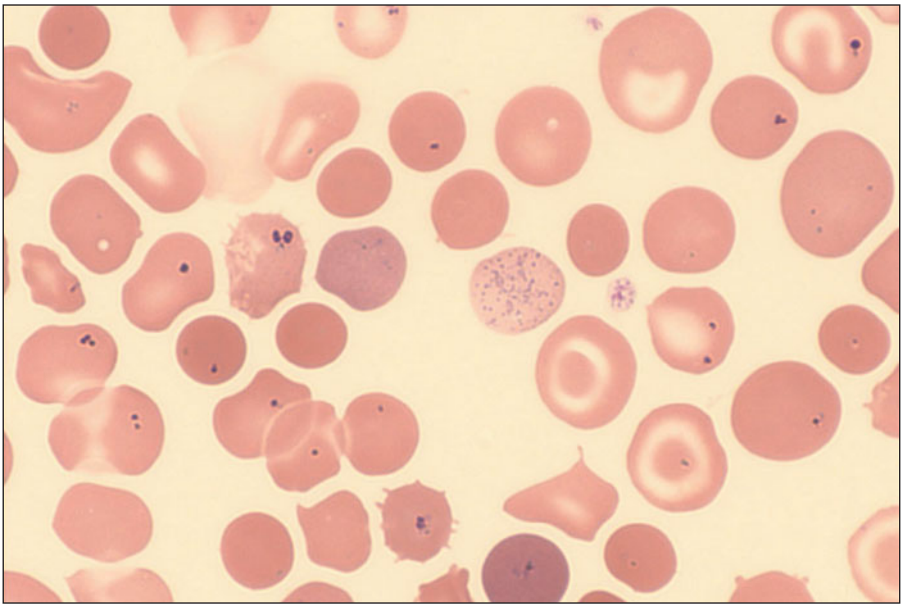


Figure IIA5-15

Peripheral blood smear—homozygous.

Clinical Features

- Common in middle and eastern Europe
- Homozygotes
  - Described as a condition that resembles thalassemia intermedia
  - Variable anemia depending on racial group
  - Symptoms develop with the first 5 years of life
  - Hepatosplenomegaly is significant
  - Skeletal abnormalities may exist also with growth retardation
- Heterozygotes
  - Mild anemia and the condition resembles thalassemia minor
  - May be asymptomatic
  - Slight splenomegaly

Pathology

- The non–α hemoglobin chain is a λ-β–globin hybrid in which the N-terminal end of the λ chain is fused to the C-terminal end of a β chain
- Believed to arise during meiosis from aberrant recombination of misaligned λ and β chains on separate chromosomes
- Two hybrid chains combine with two α chains to form hemoglobin Lepore
- Hemoglobin Lepore is stable and has normal functional properties, except a slight increase in oxygen
- The abnormal chains are ineffectively synthesized, leading to an excess of α chains that precipitate, leading to cell membrane damage in inflexibility—hemolytic anemia is the result

Laboratory Features

Homozygotes

- Hemoglobin level is usually 4.0–11.0 g/dL
- Microcytic, hypochromic anemia
- Anisocytosis poikilocytosis, codocytes, basophilic stippling, Pappenheimer bodies

Heterozygotes

- Hemoglobin level is slightly decreased
- Microcytic, hypochromic anemia

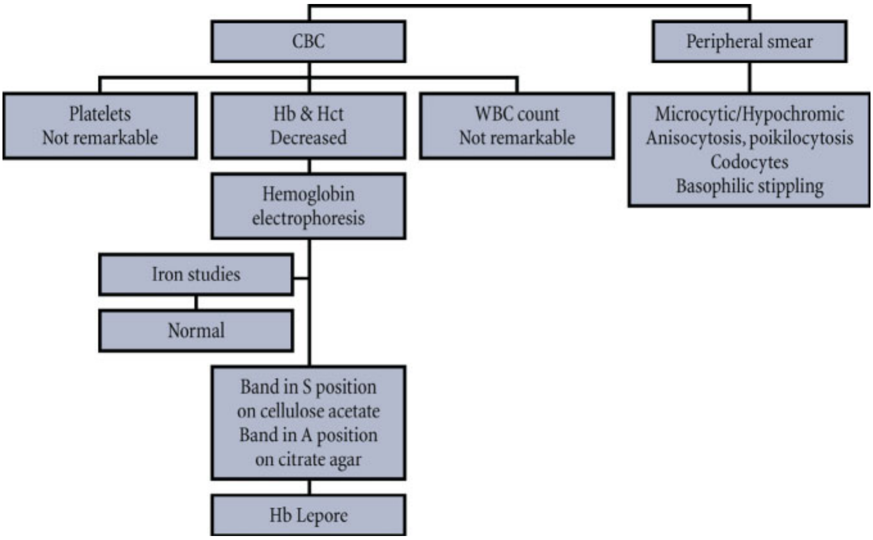
Bone Marrow

- Erythroid marrow expands and produces abnormal cells
- Ineffective erythropoiesis contributes to the anemia as the abnormal cells are destroyed

Hemoglobin Electrophoresis (Cellulose Acetate, pH 8.4)

- Homozygotes
  - 0% hemoglobin A
  - 0% hemoglobin A_2
  - 75% hemoglobin F
  - 25% hemoglobin Lepore (hemoglobin Lepore migrates like hemoglobin S)
- Heterozygotes
  - 75–85% hemoglobin A
  - About 2% hemoglobin A_2
  - 1–6% hemoglobin F
  - 7–15% hemoglobin Lepore

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Decreased
WBC count Not remarkable
Microcytic/Hypochromic Anisocytosis, poikilocytosis Codocytes Basophilic stippling
Hemoglobin electrophoresis
Iron studies
Normal
Band in S position on cellulose acetate Band in A position on citrate agar
Hb Lepore

HEREDITARY PERSISTENCE OF FETAL HEMOGLOBIN

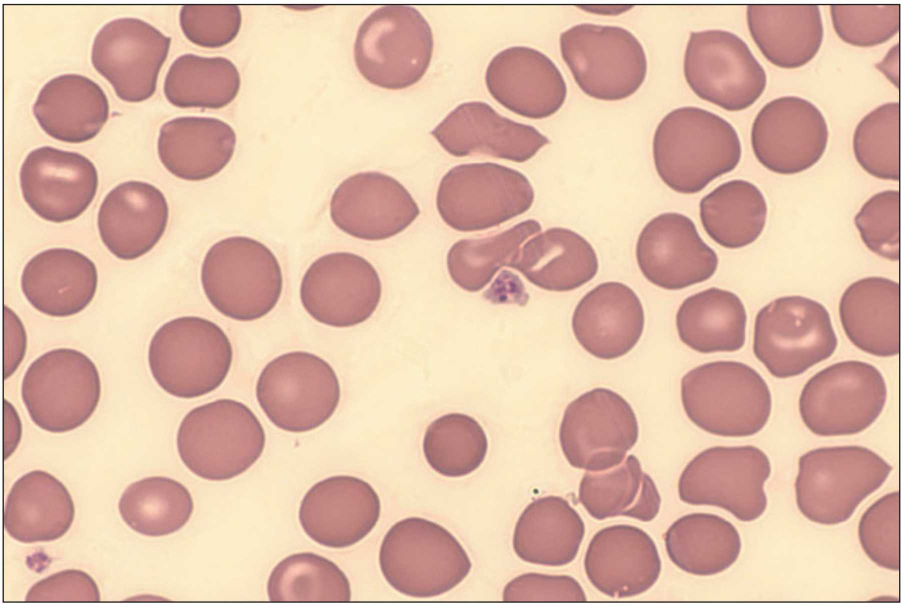


Figure IIA5-16

Peripheral blood smear.

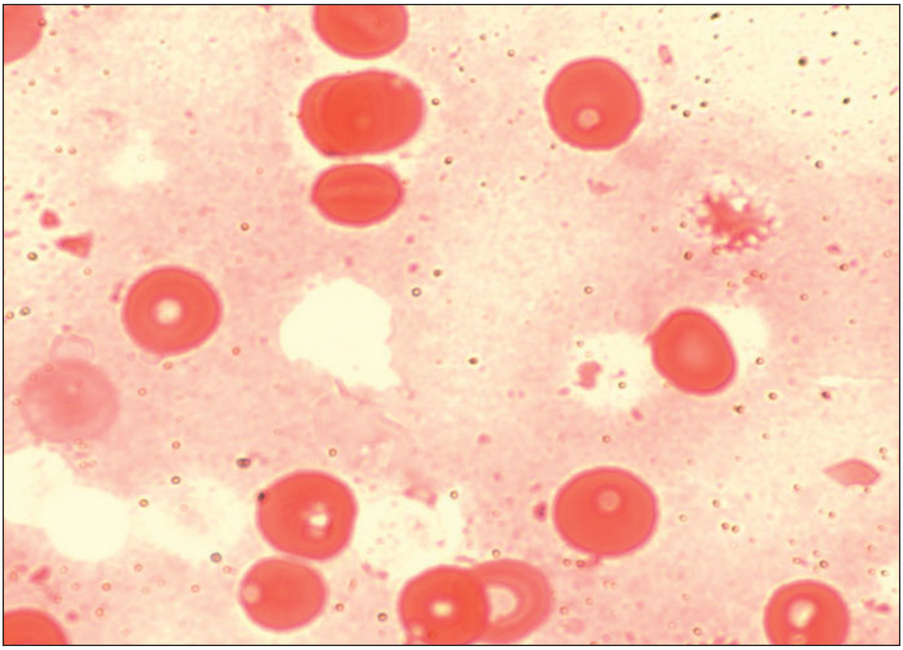


Figure IIA5-17

Kleihauer-Betke stain.

Clinical Features

- Usually no or minimal anemia
- In the homozygous state, there are no findings suggestive of thalassemia (abnormal growth, splenomegaly)

Pathology

- Deletion/inactivation of λ and β genes
- Absence of λ and β chain synthesis is compensated for by increased γ chain production into adult life, causing the increased levels of hemoglobin F
- Two types exist:
  - Pancellular (Black, Greek)
  - Heterocellular (Swiss)
- Hemoglobin F has normal to slightly higher oxygen affinity; thus, patients are usually asymptomatic
- Slightly increased oxygen affinity will lead to increased erythropoiesis

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

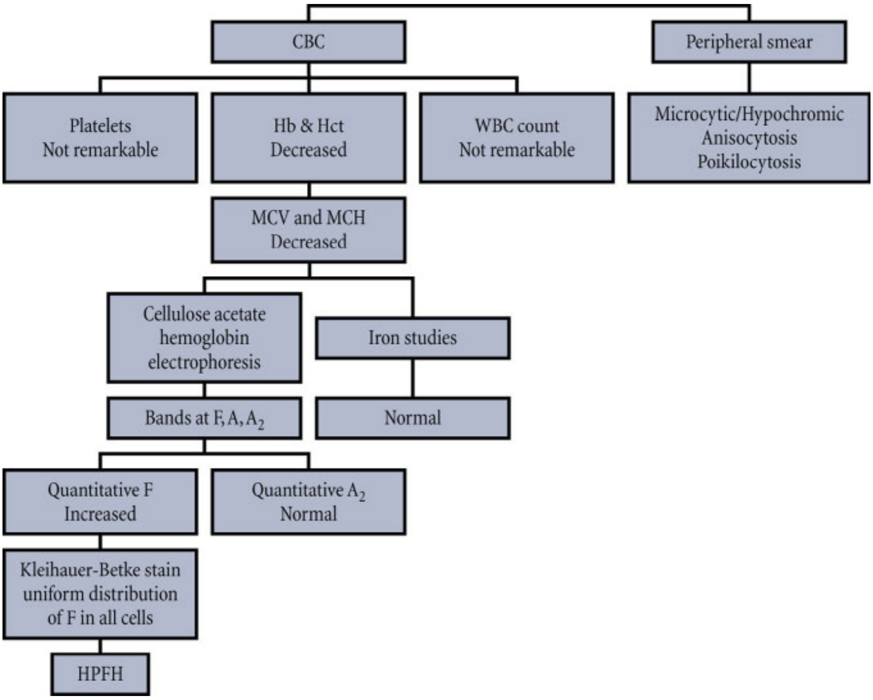
Red Blood Cells

- Microcytic/hypochromic anemia
- Mild erythrocytosis
- Mean corpuscular volume decreased
- Anisocytosis
- Poikilocytosis
- Target cells present

Hemoglobin Electrophoresis

- Homozygotes
  - 100% hemoglobin F
- Heterozygotes
  - 10–30% hemoglobin F
  - 1–2% hemoglobin A_2

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Decreased
WBC count Not remarkable
Microcytic/Hypochromic Anisocytosis Poikilocytosis
MCV and MCH Decreased
Cellulose acetate hemoglobin electrophoresis
Iron studies
Bands at F, A, A_2
Normal
Quantitative F Increased
Quantitative A_2 Normal
Kleihauer-Betke stain uniform distribution of F in all cells
HPFH

HEMOGLOBIN S

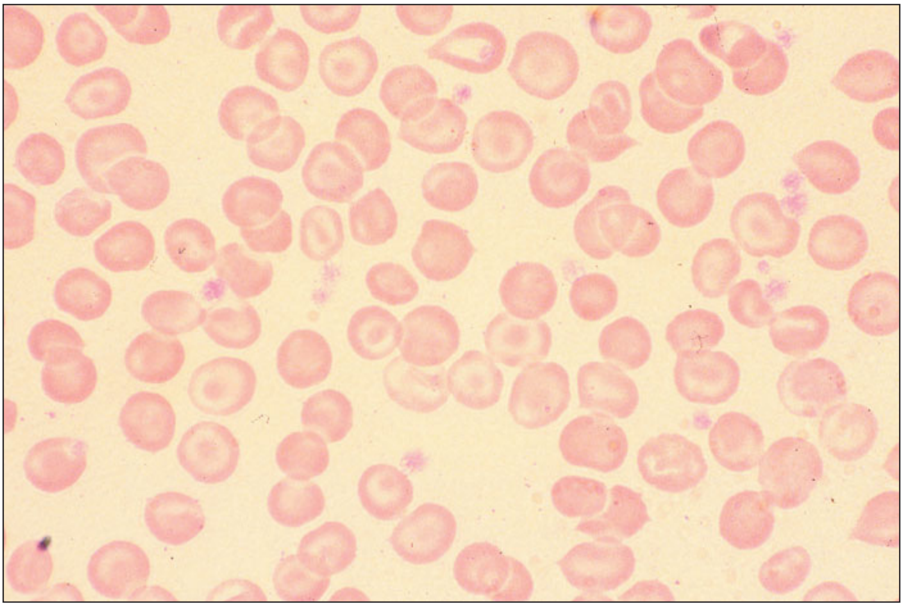


Figure IIA5-18

Peripheral blood smear—heterozygous.

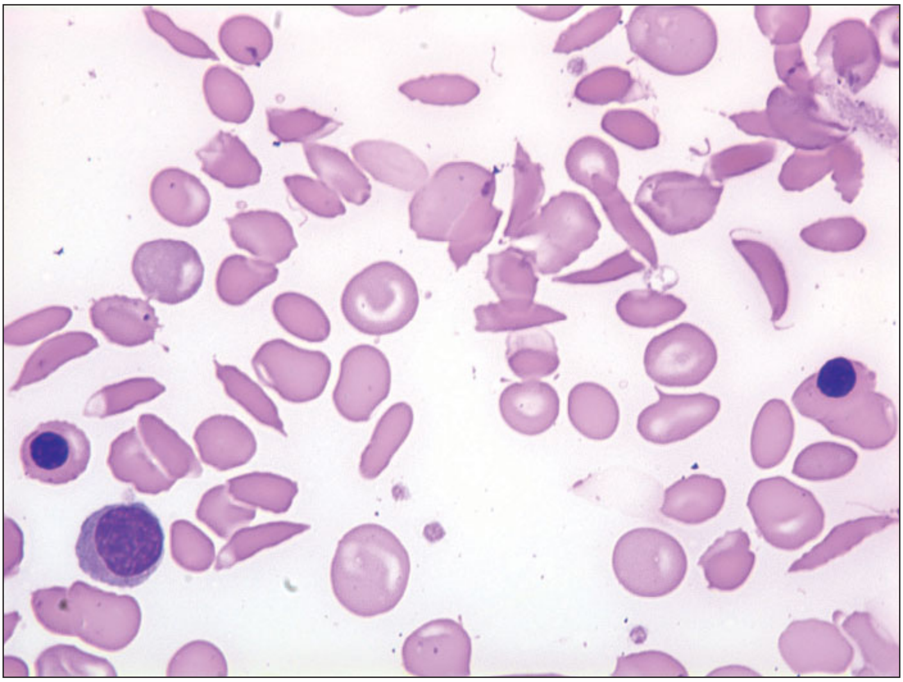


Figure IIA5-19

Peripheral blood smear—homozygous.

Clinical Features

- Homozygous
  - A disease state that occurs in approximately 0.3–1.3% of American Blacks
  - Person with this disorder may present with fever, effusion of joints, bone deformities, loss of renal function, priapism, enlarged liver, ocular manifestations, leg ulcers, frequent infections, decreased spleen function, complications during pregnancy, and/or cerebrovascular accidents
  - Acute episodes may be manifest
- Heterozygous
  - The individual possesses one normal beta gene and one S gene
  - In American Blacks, the frequency is approximately 8%
  - No clinical symptoms are associated with the trait, but episodes of hematuria may occur

Pathology

- A single nucleotide base change in the codon responsible for the synthesis of the sixth amino acid in the β-globulin chain, resulting in the substitution of valine for glutamic acid
- The deoxyhemoglobin polymerizes within the red blood cell
- Extravascular hemolysis of sickled cells takes place, causing a chronic hemolytic anemia

Laboratory Features

Homozygous

White Blood Cells

- Usually increased during a crisis, may be up to 25×10^9/L

Platelets

- Normal to increased

Red Blood Cells

- Normocytic/normochromic anemia
- Hemoglobin level 6.5–10.0 g/dL
- Reticulocyte count is increased (10–20%)
- Red blood cell distribution width is increased
- Smear shows polychromasia, codocytes, Howell-Jolly bodies, nucleated red blood cells, and drepanocytes

Bone Marrow

- Erythroid hyperplasia caused by chronic hemolysis

Hemoglobin Electrophoresis

- 0% hemoglobin A
- 80–99% hemoglobin S
- Slightly increased hemoglobin A_2
- 1–20% hemoglobin F

Heterozygous

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

Red Blood Cells

- Codocytes
- Hemoglobin and hematocrit levels normal

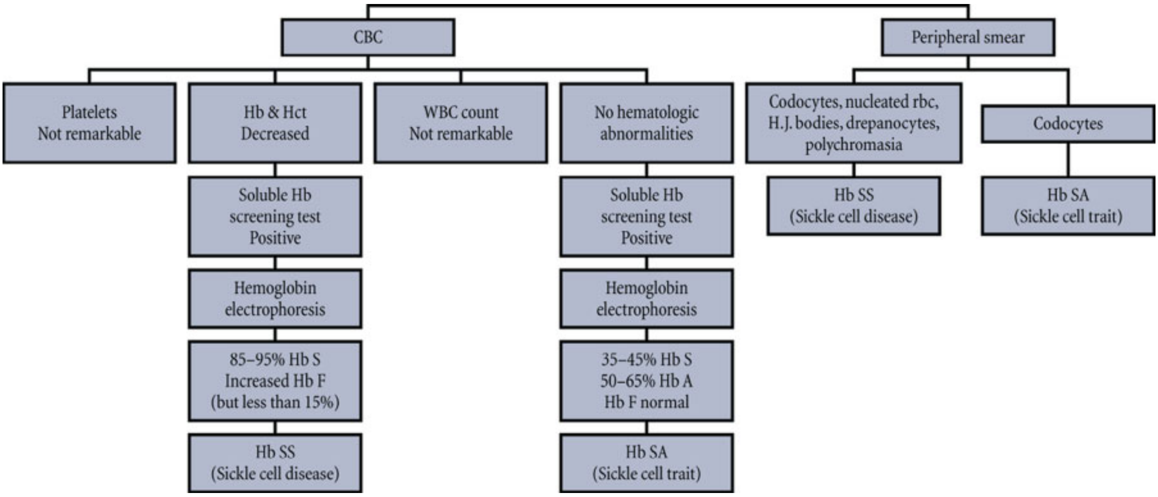
Bone Marrow

- Not remarkable

Hemoglobin Electrophoresis

- 50–65% hemoglobin A
- 35–45% hemoglobin S
- Normal to slightly increased hemoglobin A_2
- Normal hemoglobin F

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Decreased
WBC count Not remarkable
No hematologic abnormalities
Codocytes, nucleated rbc, H.J. bodies, drepanocytes, polychromasia
Codocytes
Soluble Hb screening test Positive
Soluble Hb screening test Positive
Hb SS (Sickle cell disease)
Hb SA (Sickle cell trait)
Hemoglobin electrophoresis
Hemoglobin electrophoresis
85–95% Hb S Increased Hb F (but less than 15%)
35–45% Hb S 50–65% Hb A Hb F normal
Hb SS (Sickle cell disease)
Hb SA (Sickle cell trait)

HEMOGLOBIN S/β THALASSEMIA

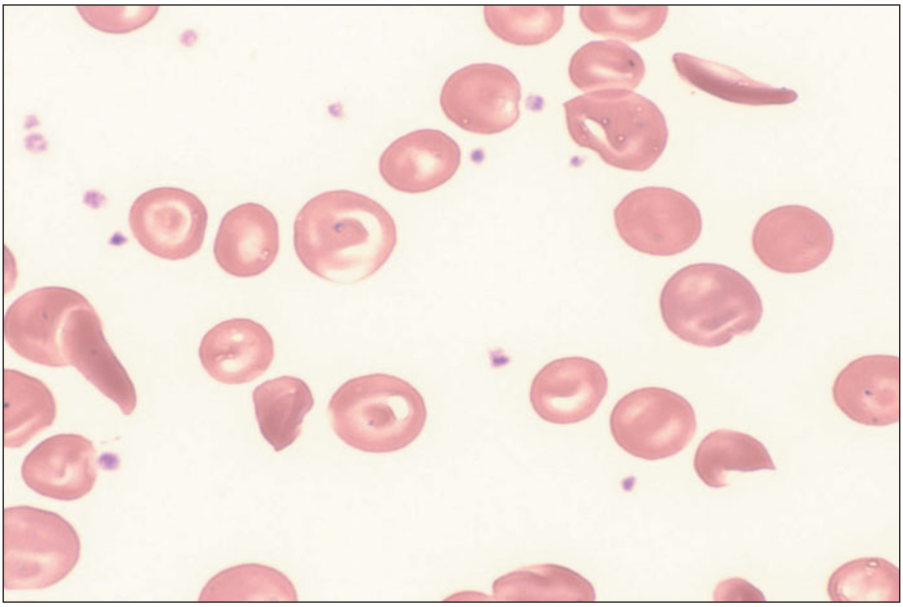


Figure IIA5-20

Peripheral blood smear.

Clinical Features

- S/β^0—severity comparable to that seen in sickle cell anemia
- S/β^+—milder clinical course comparable to SC disease
- Splenomegaly

Pathology

- β thalassemia gene reduces the rate of synthesis of beta^A chain, resulting in a predominance of beta^S

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

Red Blood Cells

- Microcytic/hypochromic anemia
- Decreased mean corpuscular volume

Hemoglobin Electrophoresis

- S/β^0—mostly hemoglobin S, increased A_2, variable F and no A
- S/β^+—hemoglobin S about 11%, A_2 about 6%

HEMOGLOBIN S/C DISEASE

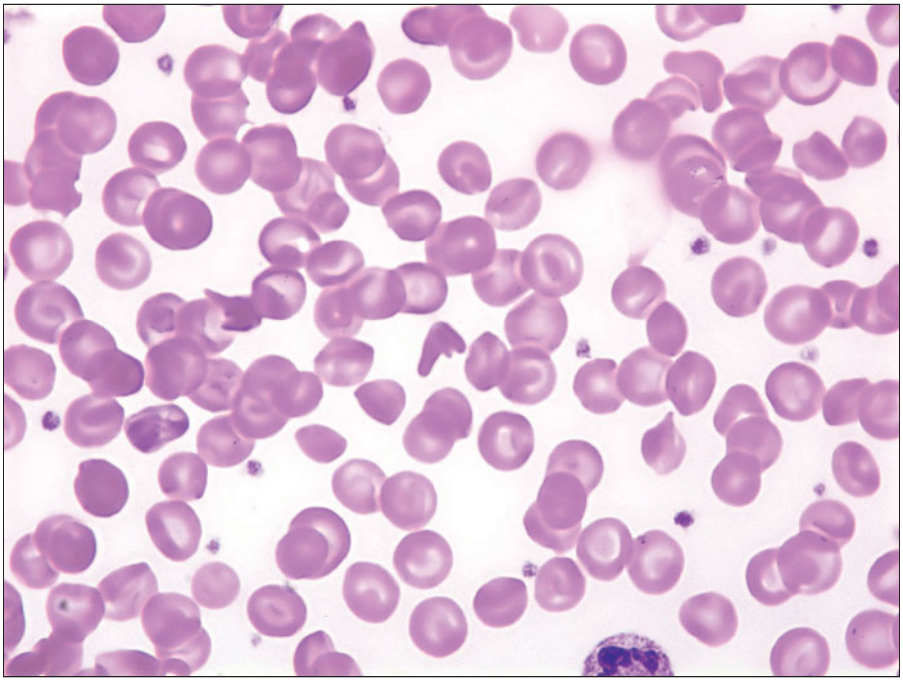


Figure IIA5-21

Peripheral blood smear.

Clinical Features

- Splenomegaly
- Proliferative retinopathy
- Aseptic necrosis of long bones
- Muscle, bone, and joint pain
- Hematuria
- Acute pulmonary disease
- Splenic infarction
- Vaso-occlusive crisis during pregnancy, surgery, or medical emergency

Pathology

- Both β chains are abnormal
- Less frequent and less severe than sickle cell anemia
- More severe than sickle trait of C trait

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

Red Blood Cells

- Knizocytes, stomatocytes, and target cells present
- Increased mean corpuscular hemoglobin
- Microcytic anemia
- Sickling not prominent
- SC crystals

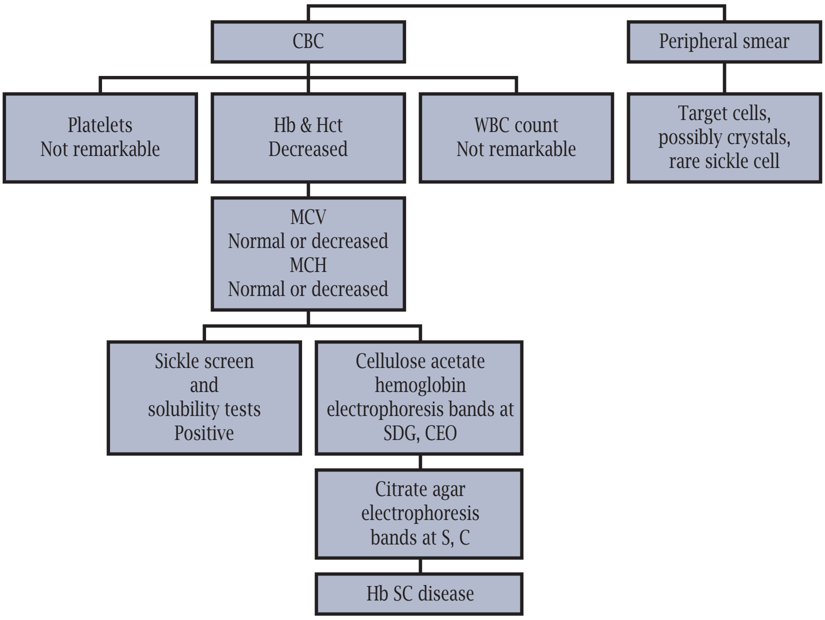
Bone Marrow

- Normoblastic hyperplasia

Hemoglobin Electrophoresis

- Equal amounts of hemoglobin S and hemoglobin C
- 1–2% hemoglobin F
- Trace of A_2

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Decreased
WBC count Not remarkable
Target cells, possibly crystals, rare sickle cell
MCV Normal or decreased MCH Normal or decreased
Sickle screen and solubility tests Positive
Cellulose acetate hemoglobin electrophoresis bands at SDG, CEO
Citrate agar electrophoresis bands at S, C
Hb SC disease

UNSTABLE HEMOGLOBINS

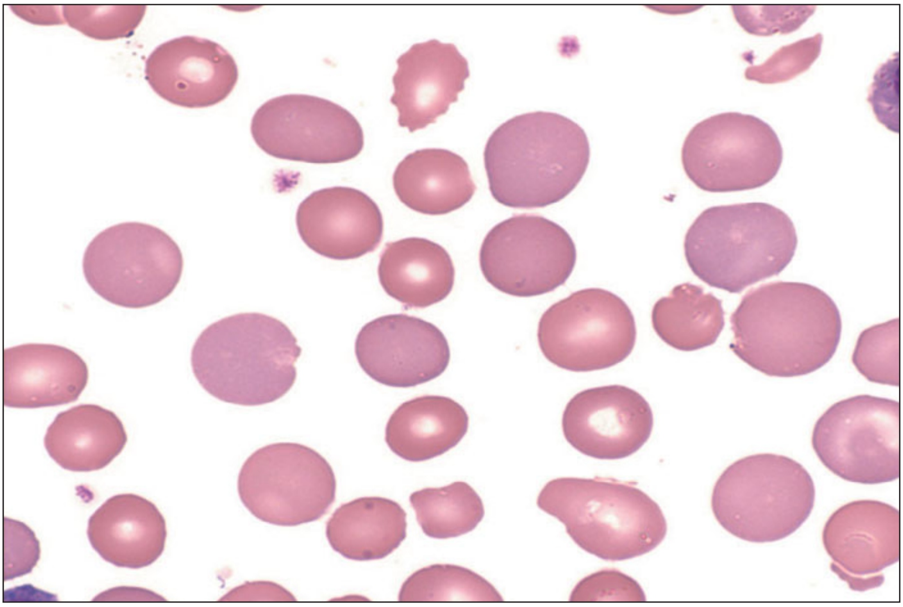


Figure **IIA5-22**

Peripheral blood smear.

Clinical Features

- Hemoglobin denaturation and hemolysis may occur spontaneously
- Symptoms may occur only after drug administration, infection, or other changes to the normal environment
- Jaundice and splenomegaly occur because of increased red blood cell hemolysis
- Excretion of dark urine
- Cyanosis may result from the formation of sulfhemoglobin
- Methemoglobin

Pathology

- Amino acid substitutions in critical internal portions of the globin chains
- Abnormal hemoglobin precipitates as Heinz bodies, which attach to the inner surface of the membrane and can cause cell rigidity, membrane damage, and, thus, erythrocyte hemolysis
- Homozygous state is incompatible with life
- Oxygen stability may be increased or decreased depending on where the amino acid substitution is located
- Hemoglobin with high oxygen affinity is usually accompanied by erythrocytosis
  - Oxygen dissociation curve is shifted to the left
  - Decreased amount of oxygen released to the tissues and increased erythropoietin levels
- Hemoglobin with decreased oxygen affinity may be asymptomatic
  - Oxygen dissociation curve is shifted to the right
  - Increased amount of oxygen delivered to the tissues

Laboratory Features

White Blood Cells

- Not remarkable

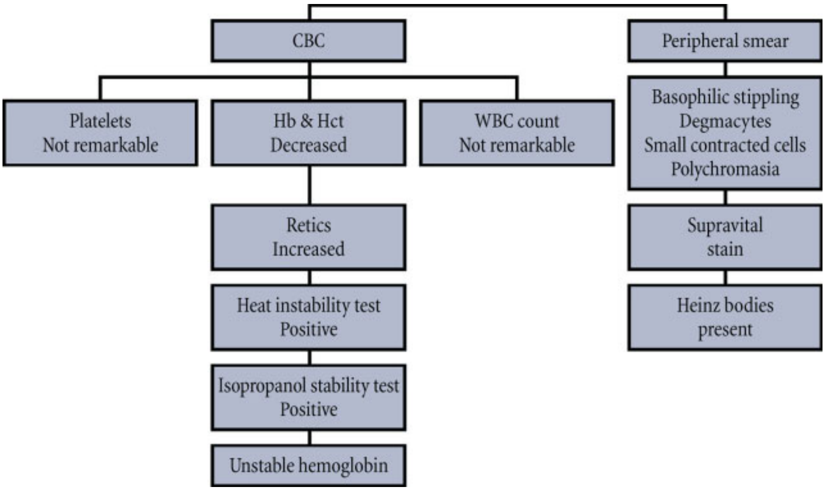
Platelets

- Not remarkable

Red Blood Cells

- Normochromic/normocytic anemia
- Slight decrease in mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration
- Reticulocyte count is increased
- Basophilic stippling, bite cells, and small contracted cells may be present
- Osmotic fragility abnormal after 24-hour incubation
- Heat instability test result is positive
- Isopropanol stability test result is positive
- Hemoglobin electrophoresis is abnormal in about 45% of cases—A_2 and F are sometimes increased
- Heinz bodies are seen on brilliant cresyl blue stain

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Decreased
WBC count Not remarkable
Basophilic stippling Degmacytes Small contracted cells Polychromasia
Retics Increased
Supravital stain
Heat instability test Positive
Heinz bodies present
Isopropanol stability test Positive
Unstable hemoglobin

CHAPTER 6

Hemolytic Anemias

COLD AGGLUTININ DISEASE

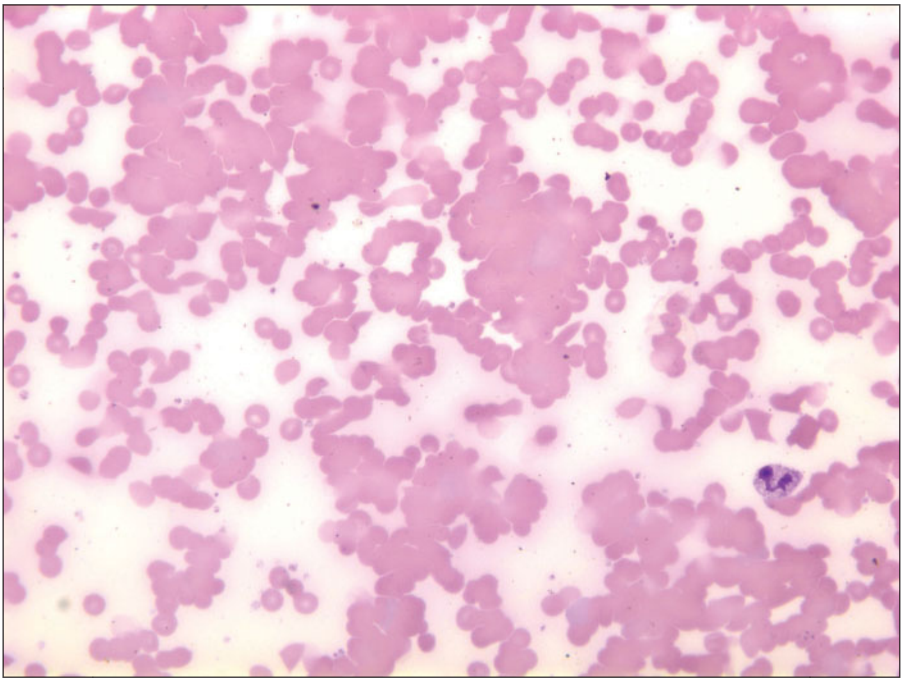


Figure IIA6-1

Peripheral blood smear.

Clinical Features

- Peak incidence in patients older than 50 years
- Onset may be sudden and severe, but the syndrome usually does not last >1–3 weeks
- In adults, the anemia is usually gradual and not as severe as in children
- Purplish discoloration of fingers, toes, nose, ears, or other peripheral areas that are exposed to cold
- Numbness of extremities when exposed to cold
- Splenomegaly

Pathology

- Can be secondary in patients with lymphoproliferative diseases, infectious mononucleosis, or *Mycoplasma pneumoniae* infections
- Patients may develop antibodies directed against the I or i antigens on red blood cells
- Usually an IgM antibody that activates complement and hemolysis results
- In children and young adults, the syndrome is brought on by viral infections
- Diminished erythropoiesis caused by the infection

Laboratory Features

White Blood Cells

- Normal or falsely elevated

Platelets

- Not remarkable

Red Blood Cells

- Mean corpuscular volume increased when blood cools to room temperature
- Reticulocyte count increased
- Agglutination rouleaux
- Mild to moderate anisocytosis, poikilocytosis
- Polychromatophilia
- Falsely decreased red blood cell count
- Mean corpuscular hemoglobin concentration falsely increased due to falsely decreased hematocrit levels

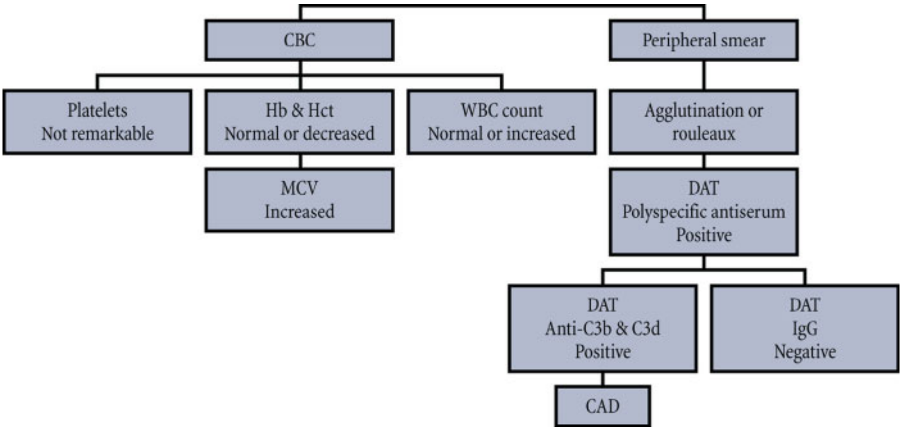
Bone Marrow

- Erythroid hyperplasia

Serological Tests

- Direct antihuman globulin test (DAT) positive, with polyspecific antisera and anti-C3d
- Cold agglutinin titer of ≥1000 in saline at 4°C.

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Normal or decreased
WBC count Normal or increased
Agglutination or rouleaux
MCV Increased
DAT Polyspecific antiserum Positive
DAT Anti-C3b & C3d Positive
DAT IgG Negative
CAD

GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

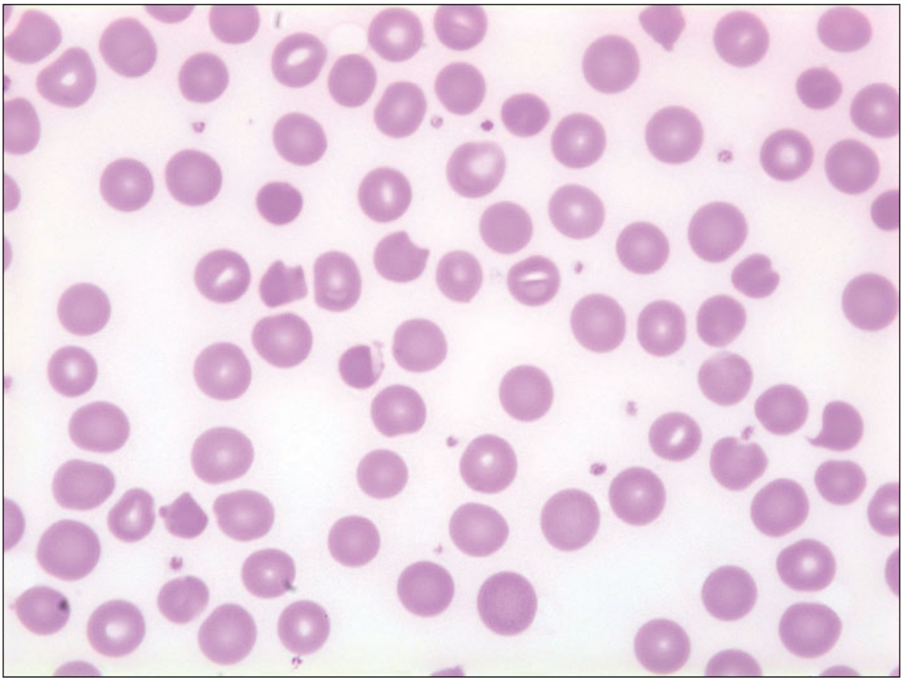


Figure IIA6-2

Peripheral blood smear.

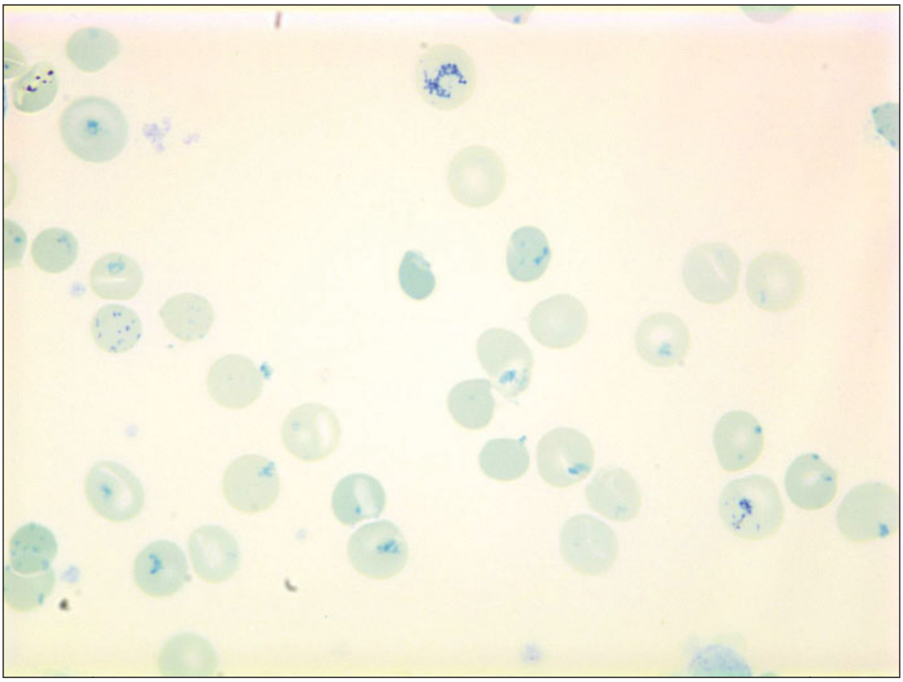


Figure IIA6-3

Brilliant cresyl blue stain.

Clinical Features

- No clinical symptoms unless exposed to chemicals or drug oxidants or severe infections
- Chronic hemolysis
- Jaundice is not prominent
- Abdominal and low back pain
- Urine is dark or black because of hemoglobinuria
- Classification is based on degree of hemolysis and enzyme deficiency
- Classes I, II, and III are clinically significant

Pathology

- The glucose-6-phosphate dehydrogenase gene is located on the X chromosome
- Red blood cells deficient in glucose-6-phosphate dehydrogenase are susceptible to oxidation and hemolysis
- Nicotinamide adenine dinucleotide phosphate production is impaired
- Build up of cellular oxidants leads to erythrocyte injury and hemolysis
- Hemoglobin is oxidized to methemoglobin, which precipitates in the form of Heinz bodies
- Heinz bodies attach to the red blood cell membrane, causing increased permeability to cations, osmotic fragility, and cell rigidity
- Red blood cells have a rigid cell wall, with the hemoglobin confined to one part of the cytosol

Laboratory Features

White Blood Cells

- Increased during attacks

Platelets

- Normal

Red Blood Cells

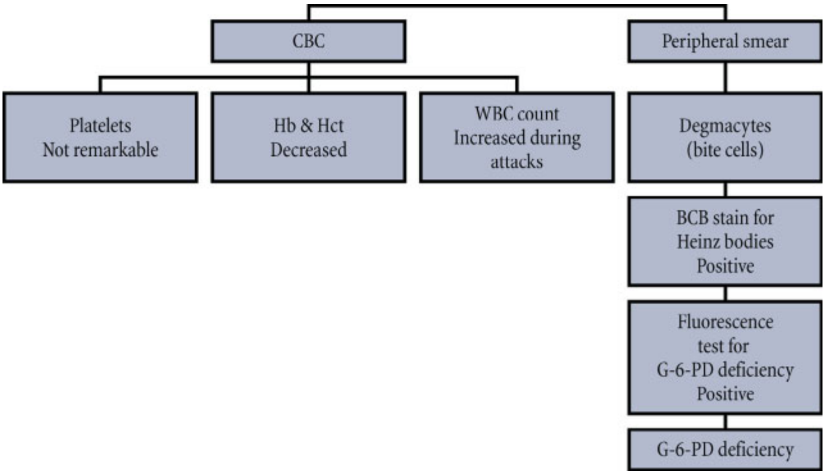
- Normocytic/normochromic anemia
- Increased reticulocyte count after hemolytic crises
- Heinz bodies
- Polychromasia
- Occasional spherocytes
- Degmacytes
- Positive fluorescent screening test result for glucose-6-phosphate dehydrogenase deficiency

- Quantitative direct enzyme assay for glucose-6-phosphate dehydrogenase decreased
- Positive Heinz body test result

Chemistries

- Indirect bilirubin and lactic dehydrogenase levels may be increased
- Haptoglobin level decreased during attacks

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Decreased
WBC count Increased during attacks
Degmacytes (bite cells)
BCB stain for Heinz bodies Positive
Fluorescence test for G-6-PD deficiency Positive
G-6-PD deficiency

HEREDITARY ACANTHOCYTOSIS

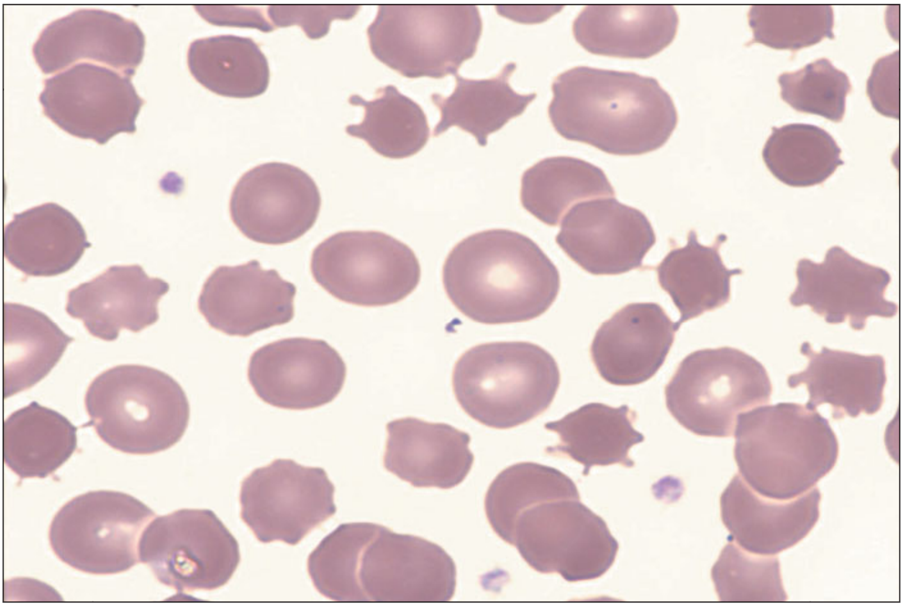


Figure IIA6-4

Peripheral blood smear.

Clinical Features

- Autosomal recessive disease
- Major symptoms due to vitamin E deficiency
- Malabsorption of fat, retinitis pigmentosa, neurologic damage, mental retardation, and delayed growth development

Pathology

- Deficiency in apoprotein
- Defect in beta lipoprotein particle assembly and secretion in the intestine and liver
- Deficient absorption and transport of fat-soluble vitamins A, D, E, and K
- Red blood cells have an increased sphingomyelin: lecithin ratio that leads to acanthocytosis
- Deficiency in triglyceride microsomal transfer protein, which is necessary for the assembly and secretion of apolipoprotein B–containing lipoproteins from the liver and intestine

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

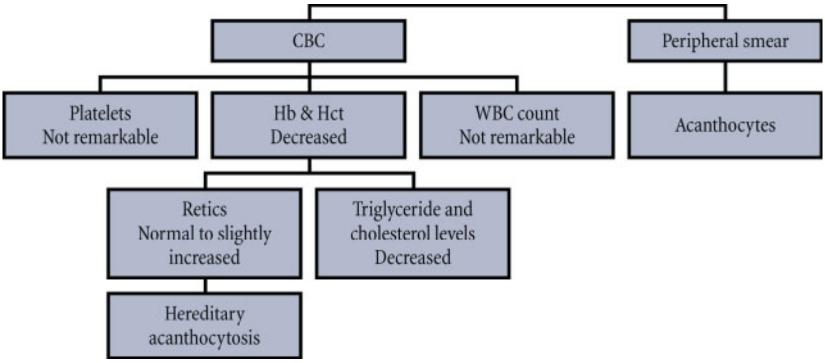
Red Blood Cells

- Mild normocytic/normochromic anemia
- Indices normal
- Reticulocyte count normal or slightly increased
- Acanthocytes
- Increased osmotic fragility

Chemistries

- Triglycerides decreased
- Cholesterol level usually <50 mg/dL
- Low-density lipoprotein, very low-density lipoprotein, chylomicrons decreased

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Decreased
WBC count Not remarkable
Acanthocytes
Retics Normal to slightly increased
Triglyceride and cholesterol levels Decreased
Hereditary acanthocytosis

HEREDITARY ELLIPTOCYTOSIS

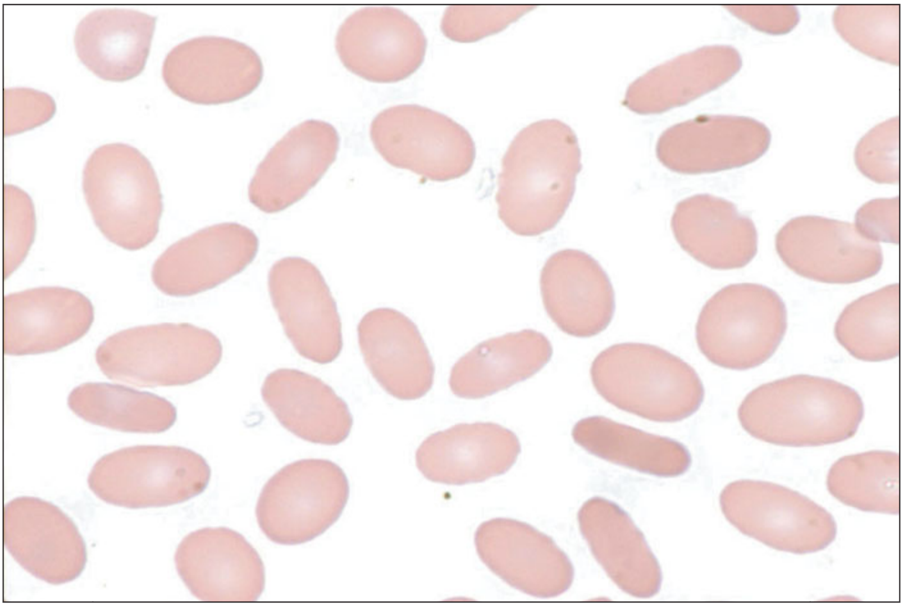


Figure IIA6-5

Peripheral blood smear—common hereditary elliptocytosis.

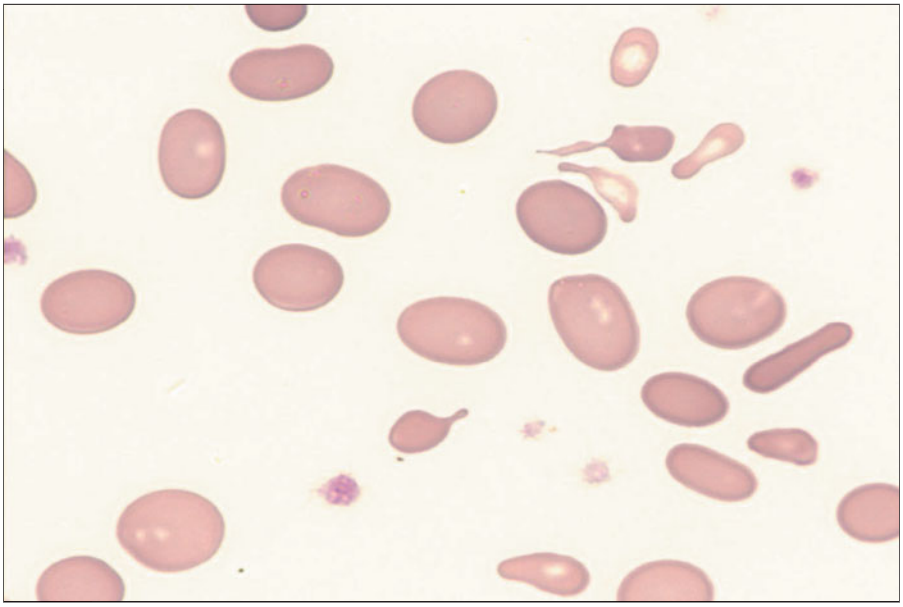


Figure IIA6-6

Peripheral blood smear—hereditary pyropoikilocytosis.

Clinical Features

- About 90% of patients show no overt signs of hemolysis
- Hemolysis is usually mild and well compensated by the bone marrow
- Morphologic classification
  - Common hereditary elliptocytosis
    - Inherited as an autosomal dominant trait
    - Ranges from asymptomatic to severe clinical disease
  - Spherocytic hereditary elliptocytosis
    - Inherited as an autosomal dominant trait
    - Presence of hemolysis
  - Stomatocytic hereditary elliptocytosis (Melanesian or Southeast Asian ovalocytosis)
    - Inherited as a recessive trait
    - Occurs in about 0.2–0.5%
    - Mild or absent hemolytic component
    - Cation permeability increased
  - Hereditary pyropoikilocytosis
    - Inherited as a recessive trait
    - Presents in infancy or early childhood
    - Microspherocytes
    - Severe red blood cell fragmentation and hemolysis
    - Hyperbilirubinemia may require exchange transfusion or phototherapy

Pathology

- The defect is in one of the skeletal proteins in the membrane, which is acquired in the circulation (horizontal membrane protein interaction)
  - Decreased associate of spectrin dimers to form tetramers due to defective spectrin chains
  - Deficient or defective band 4.1, which aids in binding spectrin to actin
  - Abnormalities of integral proteins (glycophorin C and band 3)
- Membrane fragmentation causes a decrease in cell surface and reduced cell deformability and thus a shortened life span
- Abnormal permeability to sodium and thus increased demands on adenosine triphosphate availability
- In hereditary pyropoikilocytosis, there is a mutant alpha or beta spectrin that shows severe impairment of spectrin dimer self-association and a partial deficiency of spectrin due to decreased alpha spectrin synthesis or an unstable spectrin deficiency

Laboratory Features

White Blood Cells

- Not remarkable

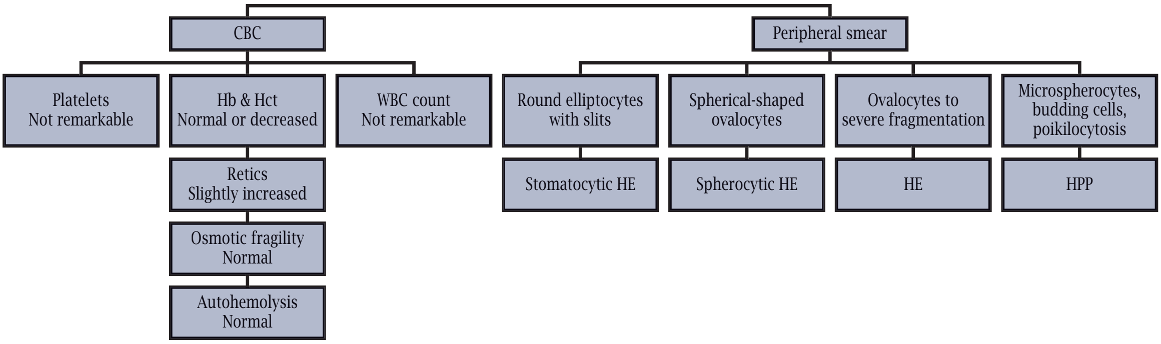
Platelets

- Not remarkable

Red Blood Cells

- Common hereditary elliptocytosis: mild elliptocytosis (15%) to severe fragmentation and poikilocytes
- Spherocytic hereditary elliptocytosis: morphology between spherocytes and elliptocytes
- Stomatocytic hereditary elliptocytosis: round elliptocytes with slit
- Hereditary pyropoikilocytosis: poikilocytosis, microspherocytes, budding of cells

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Normal or decreased
WBC count Not remarkable
Round elliptocytes with slits
Spherical-shaped ovalocytes
Ovalocytes to severe fragmentation
Microspherocytes, budding cells, poikilocytosis
Retics Slightly increased
Stomatocytic HE
Spherocytic HE
HE
HPP
Osmotic fragility Normal
Autohemolysis Normal

HEREDITARY SPHEROCYTOSIS

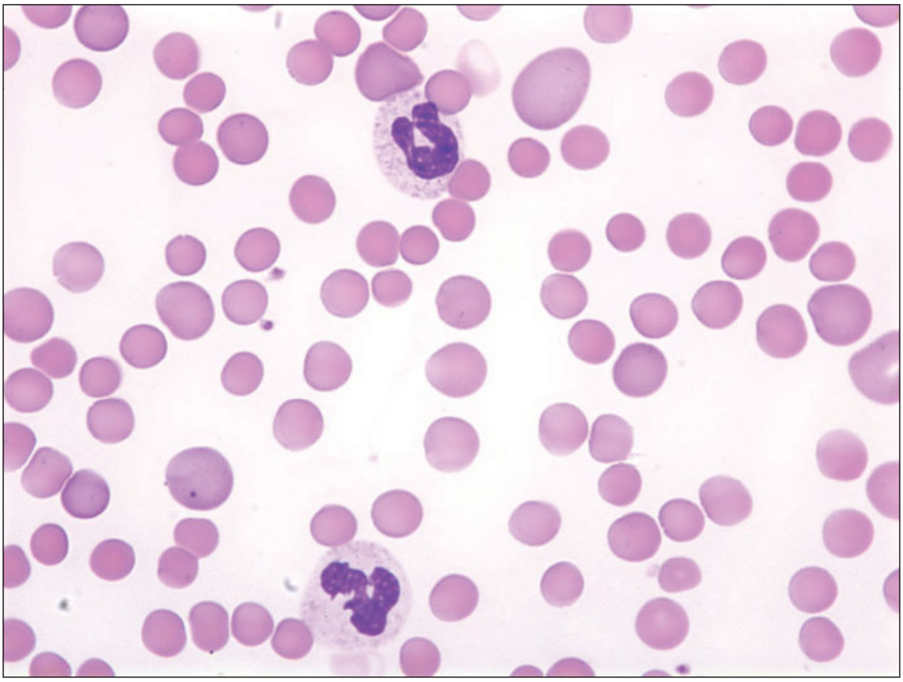


Figure IIA6-7

Peripheral blood smear.

Clinical Features

- Usually inherited as an autosomal dominant trait, but can be recessive
- Classically, the patient will have anemia, jaundice, and splenomegaly; however, the symptoms are variable
- Gallstone formation is not uncommon

Pathology

- Red blood cell membrane abnormalities
  - Spectrin deficiency
  - Ankyrin deficiency
  - Protein 3 deficiency
  - Protein 4.1 deficiency
  - Protein 4.2 defect
- Because of the membrane disorder, microspherocytes are formed that are not deformable and that are sequestered in the spleen
- A hemolytic anemia may result

Laboratory Features

White Blood Cells

- Usually normal

Platelets

- Usually normal

Red Blood Cells

- Increased mean corpuscular hemoglobin concentration
- Normal to decreased mean corpuscular volume
- Normal mean corpuscular hemoglobin
- Reticulocyte count increased (5–20%)
- Diffusely basophilic erythrocytes, spherocytes, anisocytosis, and poikilocytosis seen on smear
- Osmotic fragility increased

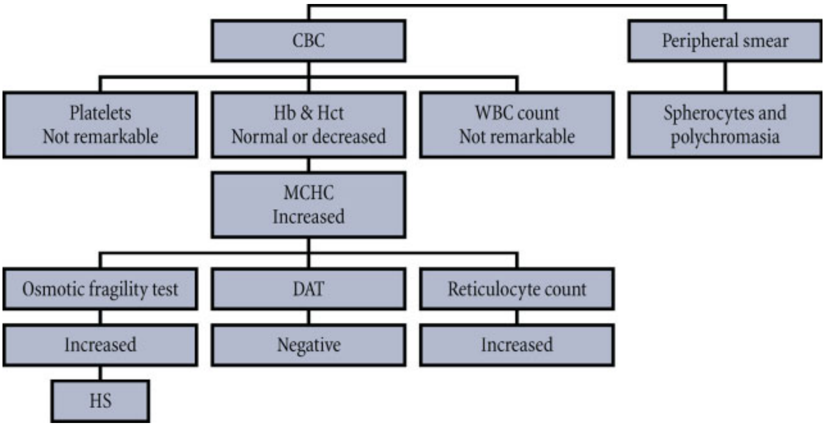
Bone Marrow

- Erythroid hyperplasia

Chemistries

- Indirect bilirubin level increased
- Fecal and urine urobilinogen levels increased
- Lactic dehydrogenase level increased
- Haptoglobin level decreased

Diagnostic Scheme


CBC
Peripheral smear
Platelets
Not remarkable
Hb & Hct
Normal or decreased
WBC count
Not remarkable
Spherocytes and polychromasia
MCHC
Increased
Osmotic fragility test
DAT
Reticulocyte count
Increased
Negative
Increased
HS

HEREDITARY STOMATOCYTOSIS

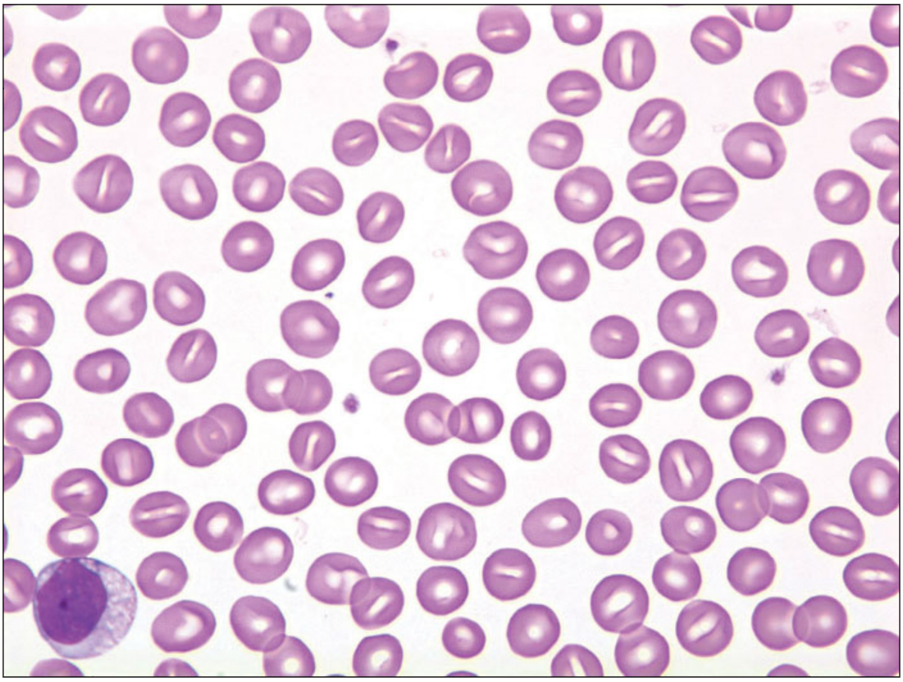


Figure IIA6-8

Peripheral blood smear.

Clinical Features

- On occasion, the patient may have a palpable spleen

Pathology

- Passive influx of sodium ions exceeds the loss of potassium ions
- The enzyme sodium-potassium adenosine triphosphatase is overwhelmed and the water content of the cell is increased
- The surface area: volume ratio is decreased
- The most common defect is one of the red blood cell membrane protein in the band 7.2b (stomatin)
- Cells are more avid, which increased thrombotic events

Laboratory Features

White Blood Cells

- Not remarkable

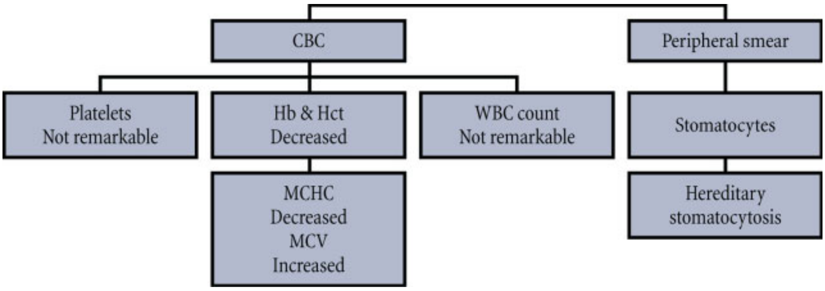
Platelets

- Not remarkable

Red Blood Cells

- Mild to moderate anemia
- Stomatocytes present
- Moderate reticulocytosis
- Increased bilirubin level
- Osmotic fragility increased
- Autohemolysis increased

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Decreased
WBC count Not remarkable
Stomatocytes
MCHC Decreased MCV Increased
Hereditary stomatocytosis

IMMUNE HEMOLYTIC ANEMIA

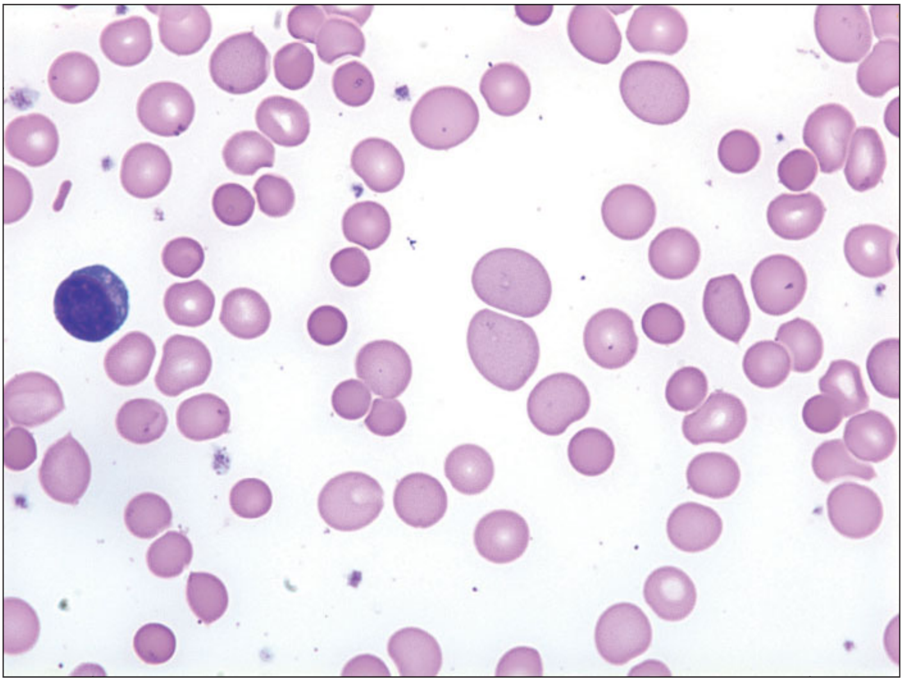


Figure IIA6-9

Peripheral blood smear.

Clinical Features

- Mild fatigue to dyspnea, syncope, and angina result because of decreased oxygen delivery to tissues
- Pallor
- Jaundice

Pathology

- Destruction of red blood cells by antibodies produced by the patient
- Destruction of red blood cells by these antibodies is brought about primarily by a mechanism that depends on immune adherence

Laboratory Features

White Blood Cells

- May be elevated due to an increase in neutrophils
- Counts may approach 30×10^9/L

Platelets

- Usually normal

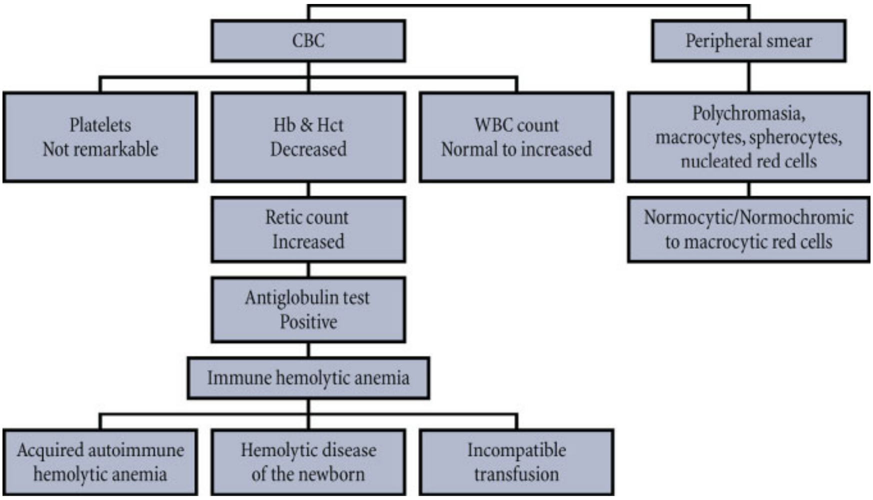
Red Blood Cells

- Hemoglobin and hematocrit levels decreased
- Normocytic/normochromic anemia
- Reticulocyte count increased
- Increased mean corpuscular volume is due to prominent reticulocytosis
- Spherocytes

Bone Marrow

- Hypercellular with erythroid precursors

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Decreased
WBC count Normal to increased
Polychromasia, macrocytes, spherocytes, nucleated red cells
Retic count Increased
Normocytic/Normochromic to macrocytic red cells
Antiglobulin test Positive
Immune hemolytic anemia
Acquired autoimmune hemolytic anemia
Hemolytic disease of the newborn
Incompatible transfusion

MICROANGIOPATHIC HEMOLYTIC ANEMIA

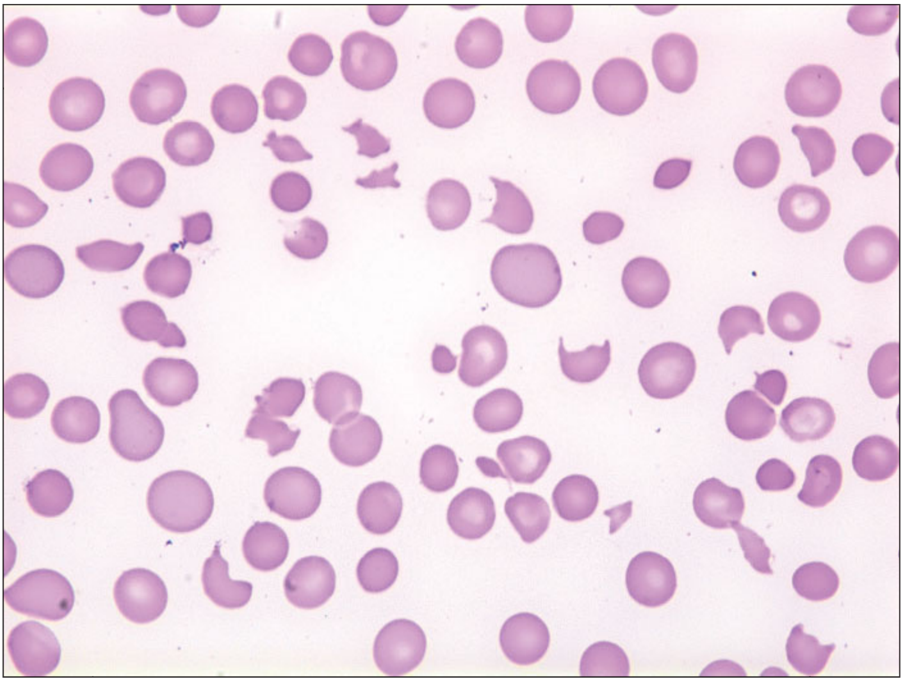


Figure IIA6-10

Peripheral blood smear.

Clinical Features

- Hemolysis—intravascular
- Thrombotic thrombocytopenic purpura
  - Occurs frequently in young adults
  - Hemorrhage into the tissues
  - Fever
  - Renal dysfunction
  - Neurologic abnormalities
- Hemolytic uremic syndrome
  - Occurs most often in children after viral illnesses
  - Fever
  - Renal failure
  - May show neurologic findings
- Disseminated intravascular coagulation
  - Associated with trauma, massive transfusion, obstetric complications, sepsis, carcinoma, and others
  - Hemorrhagic tendencies
  - Progressive renal dysfunction

Pathology

- Localized intravascular coagulation in which fibrin strands bridge the arteriolar lumen when supplying blood in inflamed or neoplastic tissue
- Fibrin strands lop off fragments of red blood cells whose membranes seal, leaving distorted cells
- In thrombotic thrombocytopenic purpura, small platelet thrombi occlude capillaries and arterioles in a variety of organs

Laboratory Features

White Blood Cells

- Not remarkable

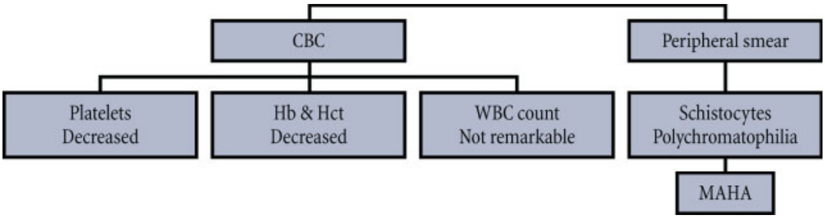
Platelets

- Decreased

Red Blood Cells

- Normocytic/normochromic anemia
- Increased reticulocyte count
- Schistocytes
- Polychromatophilia

Diagnostic Scheme


CBC
Peripheral smear
Platelets Decreased
Hb & Hct Decreased
WBC count Not remarkable
Schistocytes Polychromatophilia
MAHA

NONIMMUNE HEMOLYTIC ANEMIA

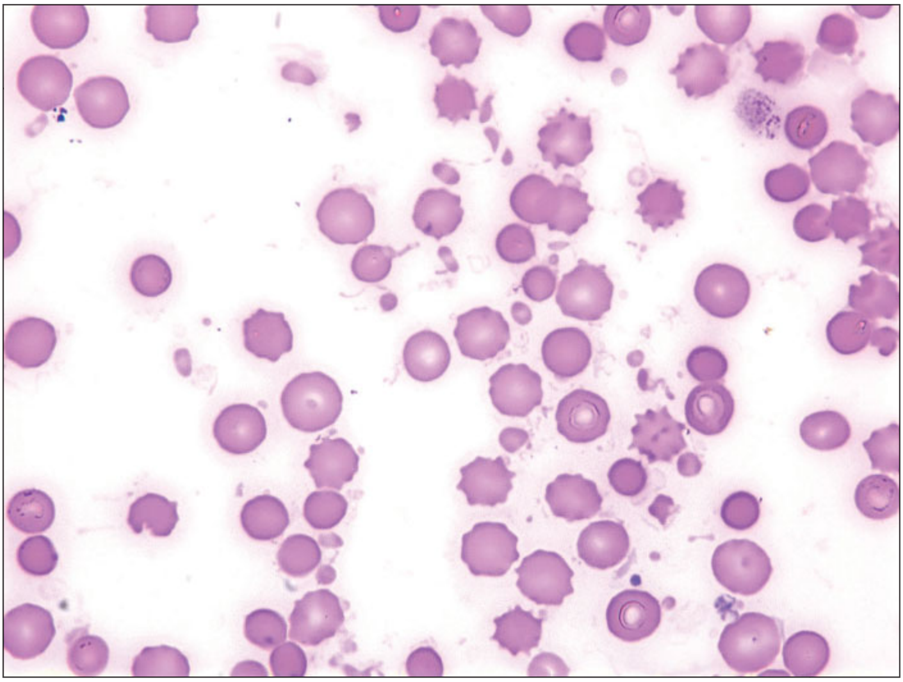


Figure **IIA6-11**

Peripheral blood smear.

Clinical Features

- Hemolysis—intravascular or extravascular
- Evidence of hemolysis—jaundice, hemoglobinuria, and hemoglobinemia

Pathology

- Thermal injury
  - Red blood cells within the vessels exposed to temperatures above about 50°C are destroyed, causing immediate intravascular fragmentation and lysis
  - Because of increased capillary permeability, plasma is lost from the vessels, resulting in hemoconcentration
- Mechanical injury
  - Red blood cells disintegrate when subjected to strong stretching or shearing forces
  - March hemoglobinuria occurs with prolonged marching or running, and red blood cells are destroyed in the vessels of the feet

Laboratory Features

Thermal Injury

White Blood Cells

- Increased

Platelets

- Not remarkable

Red Blood Cells

- Microspherocytes
- Budding of membrane

Mechanical Injury

White Blood Cells

- Not remarkable

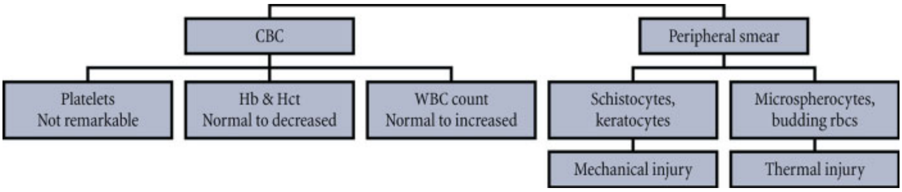
Platelets

- Not remarkable

Red Blood Cells

- Schistocytes
- Keratocytes
- Reticulocyte count increased

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Normal to decreased
WBC count Normal to increased
Schistocytes, keratocytes
Microspherocytes, budding rbcs
Mechanical injury
Thermal injury

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

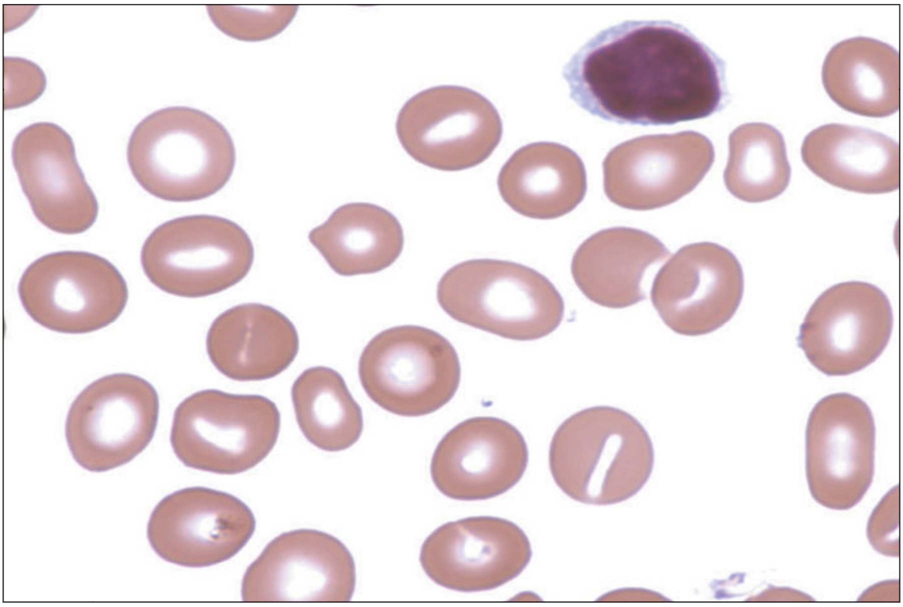


Figure IIA6-12

Peripheral blood smear.

Clinical Features

- Rare disorder with severe anemia possible
- Acute episodes of intravascular hemolysis are superimposed on a background of chronic hemolysis
- Hemoglobinuria on voiding after sleep is not a universal finding
- Recurrent venous occlusions may lead to pulmonary embolisms and hepatic and mesenteric vein thrombosis
- May be precipitated by surgery, transfusion, or infections
- Three types of paroxysmal nocturnal hemoglobinuria (PNH) cell may be observed and is associated with the severity of the disease

Pathology

- Somatic mutation in marrow stem cells
- Clonal disorder of hematopoiesis caused by a deficiency of phosphatidylinositol glycan class A
- Abnormal susceptibility to complement-mediated lysis
- The decay-accelerating factor that regulates the activity of C3 convertase is one of the missing proteins
- Loss of surface protein linkage caused by deficiency of glycophosphatidylinositol anchors
- Can progress to acute myelogenous leukemia or myelodysplasia

Laboratory Features

White Blood Cells

- Neutropenia
- Decreased leukocyte alkaline phosphatase (LAP) activity

Platelets

- Thrombocytopenia
- Abnormal platelet function

Red Blood Cells

- Hemolytic anemia
- Iron deficiency may develop with chronic hemolysis
- Acetylcholinesterase activity decreased

Bone Marrow

- Marrow hypoplasia

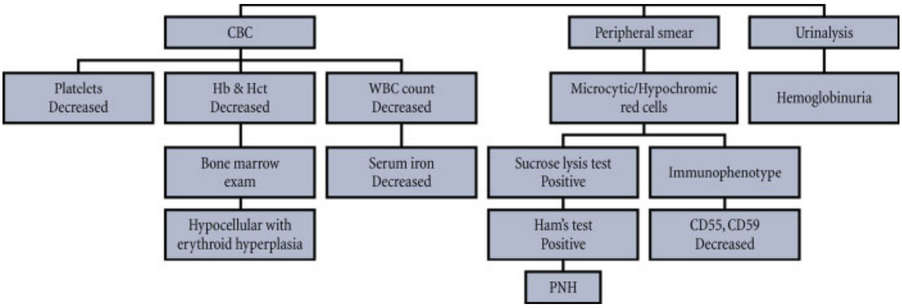
Immunophenotype

- Decreased CD55, CD59

Chemistries

- Serum haptoglobin level decreased
- Methemalbumin level increased
- Hemoglobinuria
- Hemosiderinuria
- Ham's test result positive
- Sucrose lysis test is the most common screening test

Diagnostic Scheme


CBC
Peripheral smear
Urinalysis
Platelets Decreased
Hb & Hct Decreased
WBC count Decreased
Microcytic/Hypochromic red cells
Hemoglobinuria
Bone marrow exam
Serum iron Decreased
Sucrose lysis test Positive
Immunophenotype
Hypocellular with erythroid hyperplasia
Ham's test Positive
CD55, CD59 Decreased
PNH

PYRUVATE KINASE DEFICIENCY

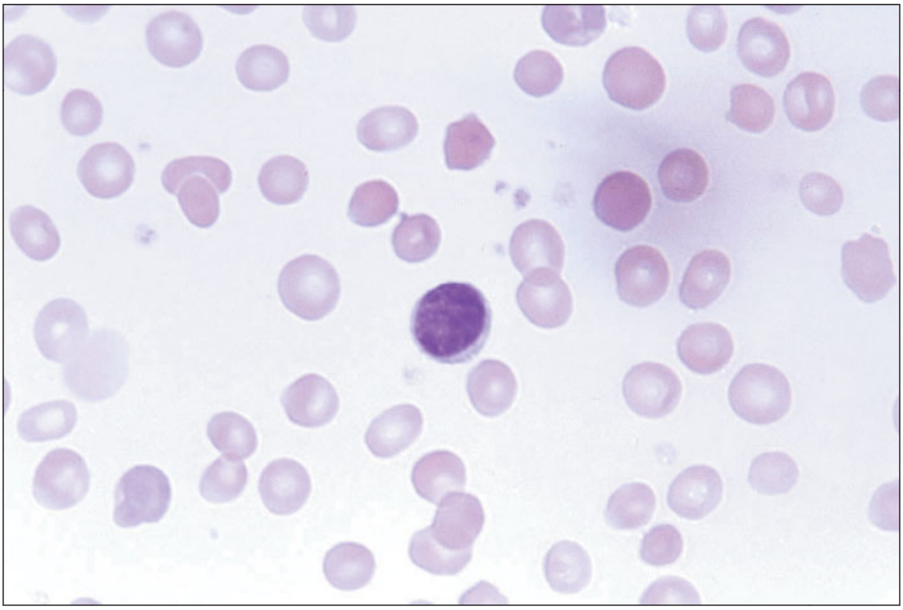


Figure IIA6-13

Peripheral blood smear.

Clinical Features

- Autosomal recessive inheritance
- Most severe types manifest in infancy
- Homozygosity produces clinical disease
- Acquired pyruvate kinase (PK) deficiency has been reported
- Severity ranges from severe neonatal anemia to asymptomatic
- May see splenomegaly, icterus, and gallstones

Pathology

- Most common enzyme deficiency in the Embden-Meyerhof pathway and second most common red blood cell enzyme deficiency
- Adenosine triphosphate levels cannot be maintained at normal levels, and the red blood cell membrane is altered
- Potassium is lost and dehydration results
- Echinocytes are formed and cannot deform in splenic cords—hemolysis results

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

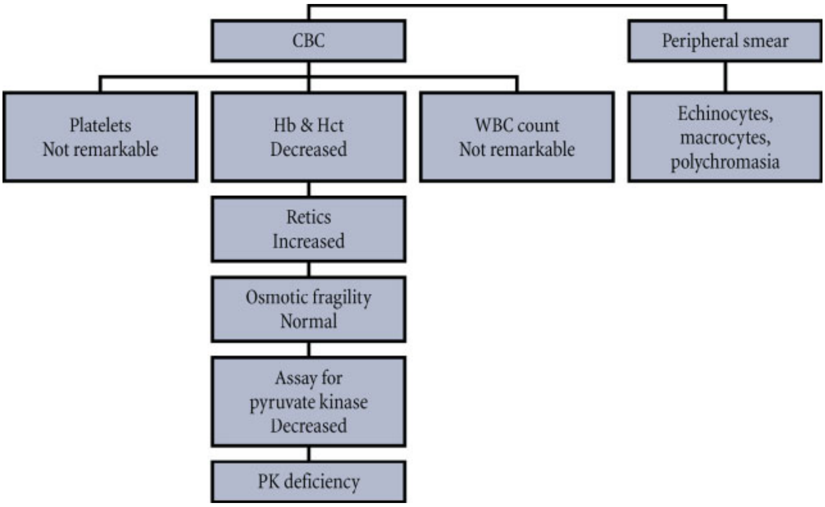
Red Blood Cells

- No characteristic cells
- May see echinocytes, macrocytes
- Increased reticulocyte count
- Normocytic/normochromic anemia
- Osmotic fragility normal

Bone Marrow

- Erythroid hyperplasia

Diagnostic Scheme


CBC
Peripheral smear
Platelets
Not remarkable
Hb & Hct
Decreased
WBC count
Not remarkable
Echinocytes,
macrocytes,
polychromasia
Retics
Increased
Osmotic fragility
Normal
Assay for
pyruvate kinase
Decreased
PK deficiency

CHAPTER 7

Acute Blood Loss

ANEMIA OF ACUTE BLOOD LOSS

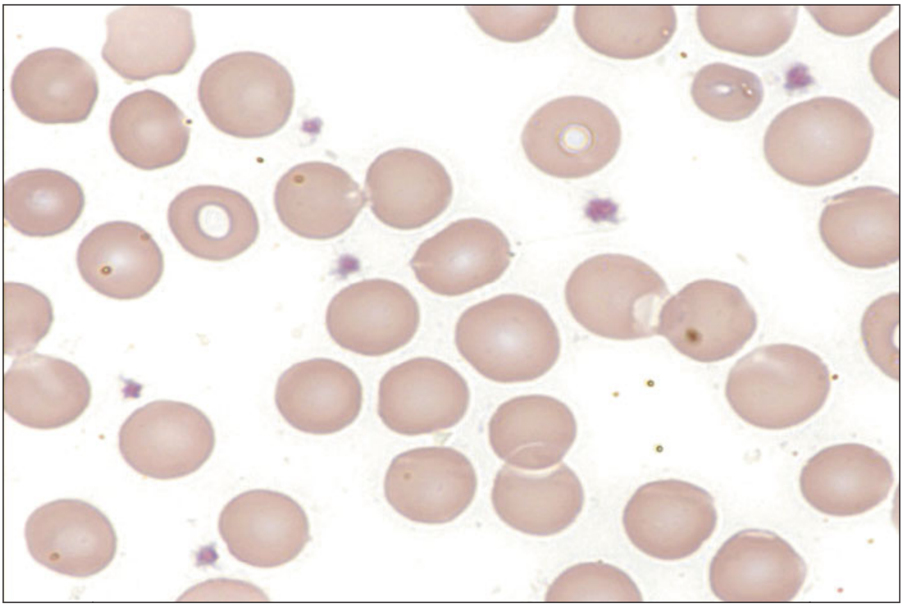


Figure IIA7-1

Peripheral blood smear.

Clinical Features

- Symptoms depend on the amount of blood loss and how fast it was lost
- Lightheadedness, hypotension, and rapid pulse
- Cool, clammy skin
- Unconsciousness and severe shock
- Death

Pathology

- An injury that allows blood to escape from blood vessels into surrounding tissues or outside the body
- If >20% of the total blood volume is lost, oxygen perfusion of tissue is disrupted, resulting in subsequent cell death

Laboratory Features (3–4 hours after the event)

White Blood Cells

- Increased with shift to the left

Platelets

- Increased

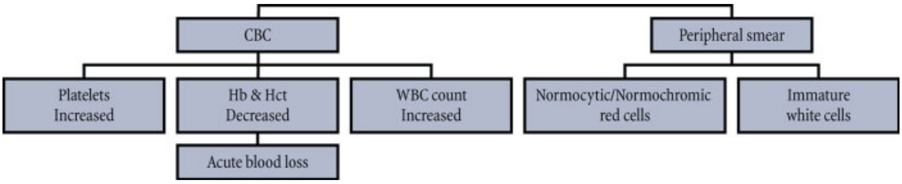
Red Blood Cells

- Hemoglobin and hematocrit levels begin to decrease
- Normocytic/normochromic anemia
- Increased reticulocytes occur 2–5 days after the event

Bone Marrow

- Erythroid hyperplasia

Diagnostic Scheme


CBC
Peripheral smear
Platelets Increased
Hb & Hct Decreased
WBC count Increased
Normocytic/Normochromic red cells
Immature white cells
Acute blood loss

CHAPTER 8

Anemias Associated With Systemic Disorders

CHRONIC RENAL DISEASE

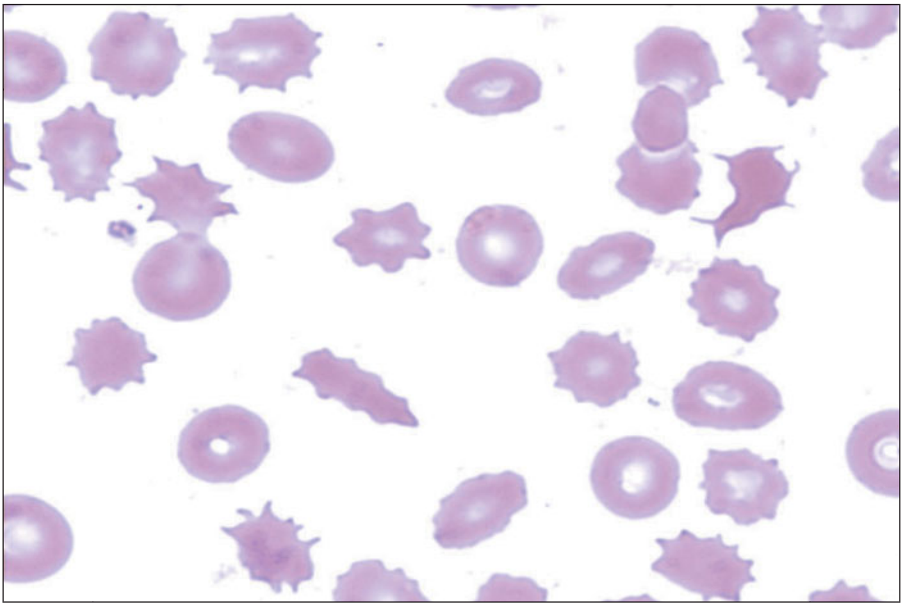


Figure IIA8-1

Peripheral blood smear.

Clinical Features

- Symptoms depend on severity of anemia
- May manifest with gastrointestinal or gynecologic bleeding
- Fatigue

Pathology

- Failure of renal excretory function and accumulation of waste products in plasma causes:
  - Decreased red blood cell survival and mild hemolytic anemia
  - Failure of renal production of erythropoietin
  - Failure of release of erythropoietin

Laboratory Features

White Blood Cells

- Not remarkable

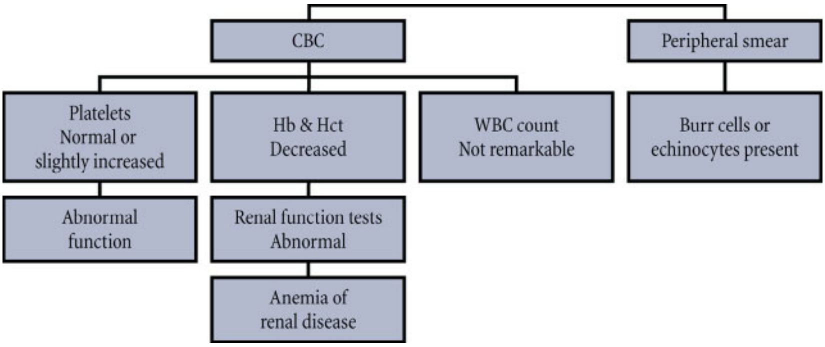
Platelets

- Normal to slightly increased
- Function may be abnormal

Red Blood Cells

- Normocytic/normochromic anemia
- Burr cells (echinocytes)
- Reticulocyte count normal

Diagnostic Scheme


CBC
Peripheral smear
Platelets Normal or slightly increased
Hb & Hct Decreased
WBC count Not remarkable
Burr cells or echinocytes present
Abnormal function
Renal function tests Abnormal
Anemia of renal disease

ENDOCRINE DISEASES

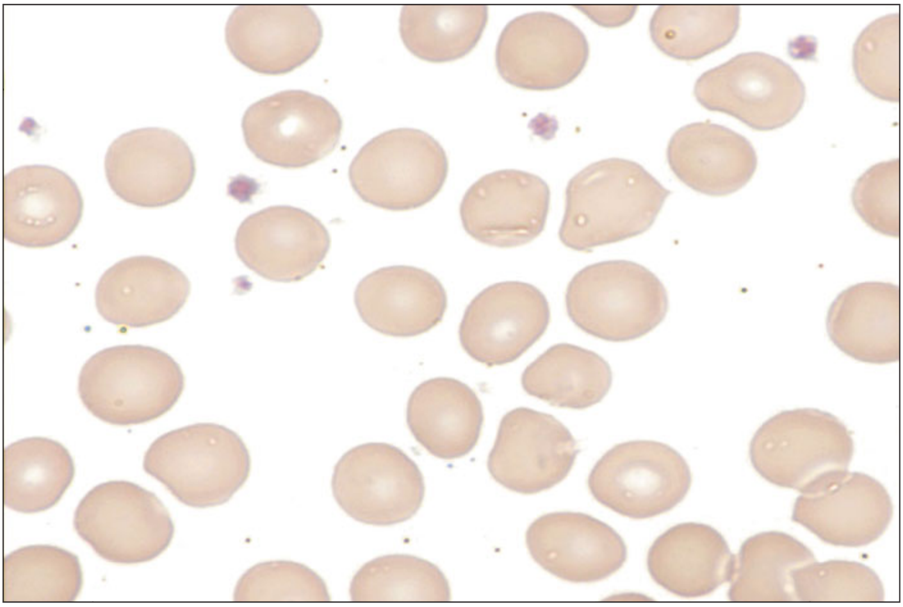


Figure **IIA8-2**

Peripheral blood smear.

Clinical Features

- Symptoms are specific to the type of endocrine disorder
  - Hyperthyroidism
  - Hypothyroidism
  - Hypercortisolism
  - Hypocortisolism
  - Hypoandrogenemia
  - Diabetes mellitus

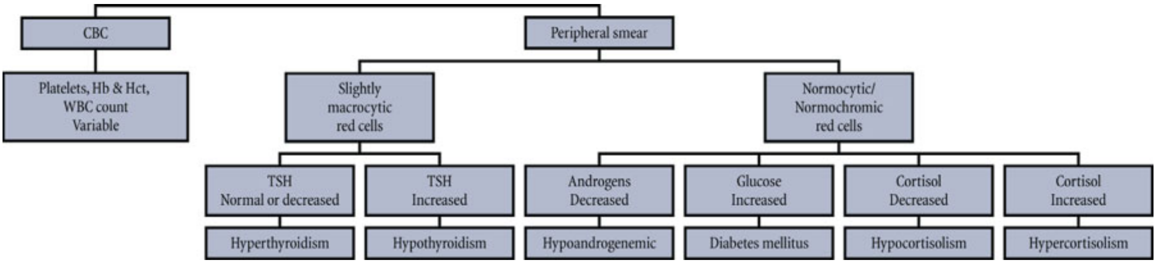
Pathology

- Hyperthyroidism
  - Elevated red blood cell mass secondary to enhanced BFU-E proliferation
  - Increased requirement for folic acid to accommodate the increased red blood cell production
- Hypothyroidism
  - Reduced red blood cell mass secondary to decreased oxygen requirements
- Hypercortisolism
  - Modest polycythemic state due to increased androgens
- Hypocortisolism
  - Hemoconcentrated state with a normal to slightly increased hematocrit level due to lack of the salt-retaining hormones
- Hypogonadism
  - Anemia due to reduced level of androgens
- Diabetes mellitus
  - Acute hemolysis may occur in ketoacidosis

Laboratory Features

- Hyperthyroidism
  - Macrocytic anemia
- Hypothyroidism
  - Usually macrocytic anemia
  - Iron-deficient anemia may occur when menorrhagia is present
- Hypercortisolism
  - Modest polycythemic picture
- Hypocortisolism
  - Normal or slightly increased hematocrit level
- Hyperandrogenemia
  - Slight normocytic/normochromic anemia
- Diabetes mellitus
  - Falsely elevated hematocrit level

Diagnostic Scheme


CBC
Peripheral smear
Platelets, Hb & Hct, WBC count Variable
Slightly macrocytic red cells
Normocytic/ Normochromic red cells
TSH Normal or decreased
TSH Increased
Androgens Decreased
Glucose Increased
Cortisol Decreased
Cortisol Increased
Hyperthyroidism
Hypothyroidism
Hypoandrogenemic
Diabetes mellitus
Hypocortisolism
Hypercortisolism

LIVER DISEASE

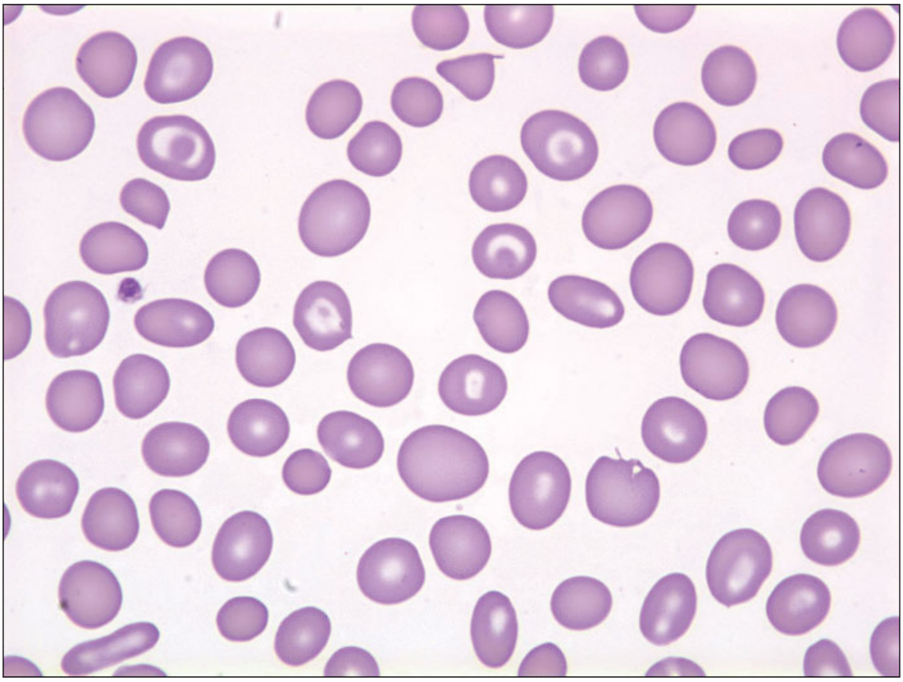


Figure IIA8-3

Peripheral blood smear.

Clinical Features

- Anemia is secondary to the abnormalities in liver function
- The most common cause of nonmegaloblastic, macrocytic anemia
- Occurs in about 50% of patients with liver disease

Pathology

- Multifaceted
  - Hemolysis
  - Impaired bone marrow response
  - Folate deficiency
  - Blood loss
- Abnormalities in red blood cell membrane lipid composition are common

Laboratory Features

White Blood Cells

- Neutropenia, neutrophilia, or lymphopenia

Platelets

- Decreased
- Abnormal function

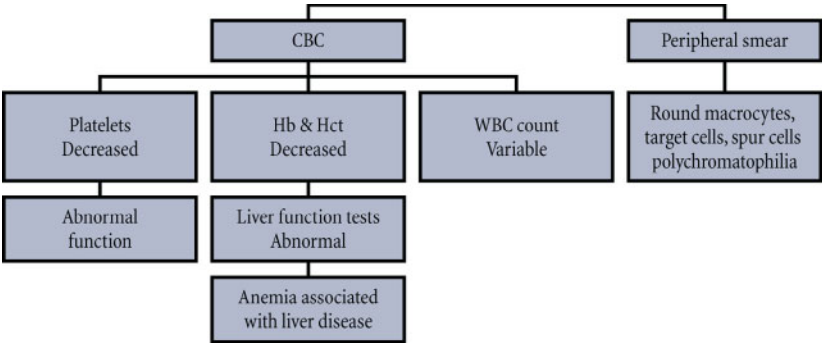
Red Blood Cells

- Mild to moderate anemia
  - Macrocytic
  - Normocytic
  - Microcytic
- Round macrocytes
- Target cells, spur cells, acanthocytes
- Increased reticulocytes

Bone Marrow

- Normocellular or hypercellular with erythroid hyperplasia
- Vacuolization of red blood cell precursors

Diagnostic Scheme


CBC
Peripheral smear
Platelets Decreased
Hb & Hct Decreased
WBC count Variable
Round macrocytes, target cells, spur cells polychromatophilia
Abnormal function
Liver function tests Abnormal
Anemia associated with liver disease

SYSTEMIC LUPUS ERYTHEMATOSUS

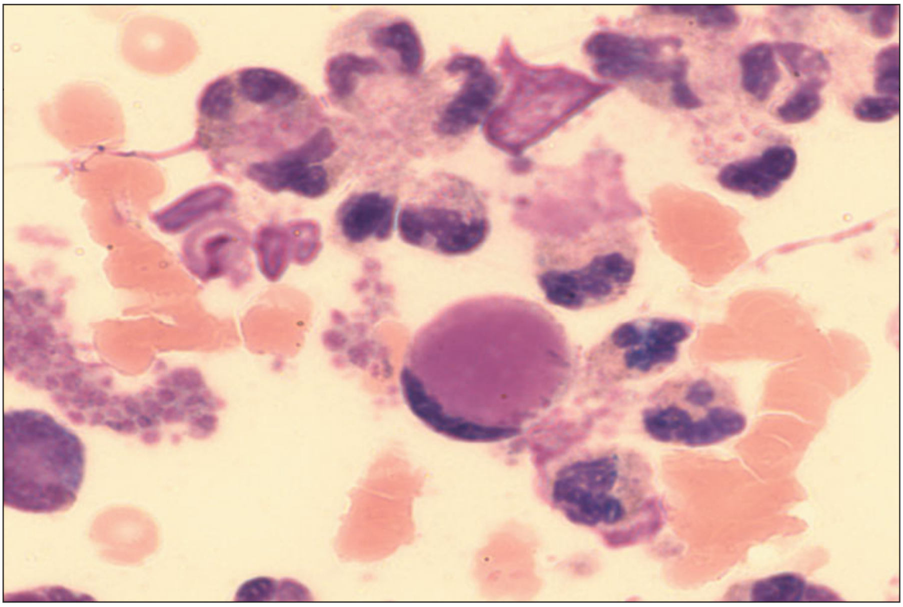


Figure IIA8-4

Buffy coat smear.

Clinical Features

- Low-grade fever
- Arthritis and arthralgia
- Skin lesions
- Nervous system disorders (psychological and neurologic changes)
- Pericarditis
- Pleuritic chest pain
- Anorexia, nausea, vomiting, and abdominal pain
- Hepatomegaly

Pathology

- Decreased cellular immunity
- Circulating immune complexes may cause tissue injury in many organ systems

Laboratory Features

White Blood Cells

- Decreased count but usually >2.0 × 10^9/L

Differential

- Normal

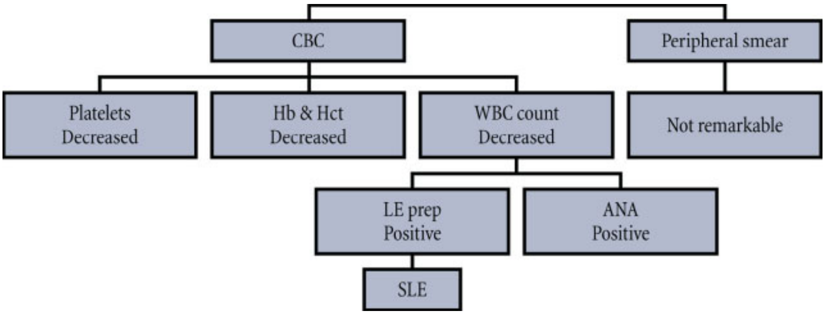
Platelets

- Decreased

Red Blood Cells

- Normocytic/normochromic anemia
- Hemolysis
  - Autoantibodies
- Circulating anticoagulants may cause prolongation of partial thromboplastin times
- Antinuclear antibodies may be present and may result in the presence of lupus erythematosus cells
- Complement levels decreased

Diagnostic Scheme


CBC
Peripheral smear
Platelets Decreased
Hb & Hct Decreased
WBC count Decreased
Not remarkable
LE prep Positive
ANA Positive
SLE

Section B

White Blood Cell Disorders

CHAPTER 1

Nonmalignant Leukocyte Disorders

BASOPHILIA

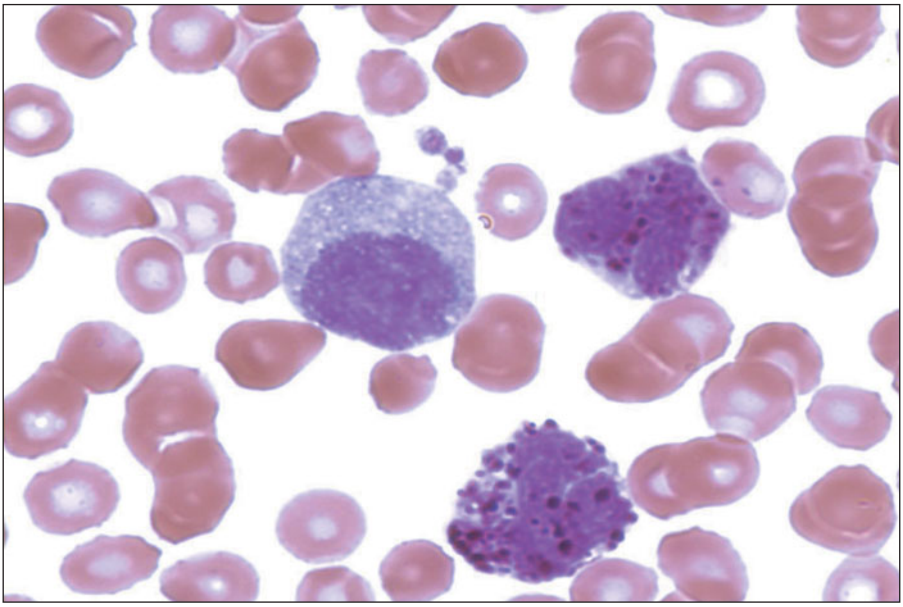


Figure IIB1-1

Peripheral blood smear.

Clinical Features

- Defined as >0.15 × 10^9/L basophils
- Varies with the etiology
  - Hypothyroidism with myxedema
  - Myeloproliferative disorders
    - Chronic myelogenous leukemia
    - Polycythemia vera
    - Primary myelofibrosis
  - After radiation exposure

Pathology

- Associated with immediate hypersensitivity reactions
  - When IgE binds to the basophil receptors, the cell degranulates and releases histamine and other inflammatory mediators
- Specific to the disorders that cause the secondary basophilia

Laboratory Features

White Blood Cells

- Increased numbers of basophils

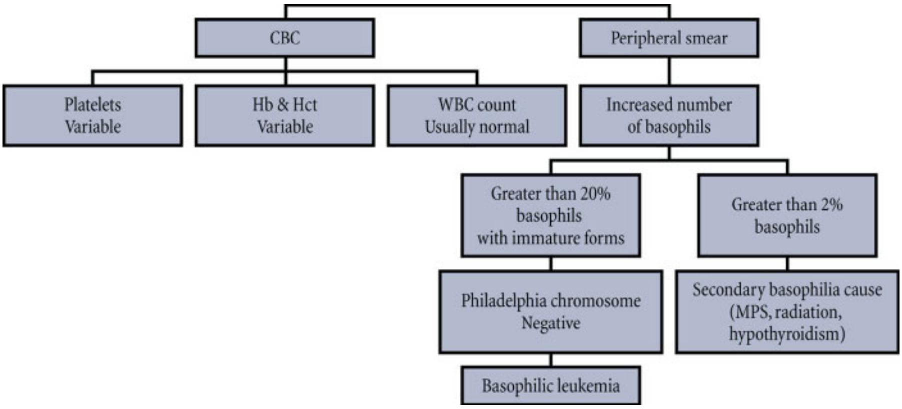
Red Blood Cells

- Variable

Platelets

- Variable

Diagnostic Scheme


CBC
Peripheral smear
Platelets Variable
Hb & Hct Variable
WBC count Usually normal
Increased number of basophils
Greater than 20% basophils with immature forms
Greater than 2% basophils
Philadelphia chromosome Negative
Secondary basophilia cause (MPS, radiation, hypothyroidism)
Basophilic leukemia

CHÉDIAK-HIGASHI ANOMALY

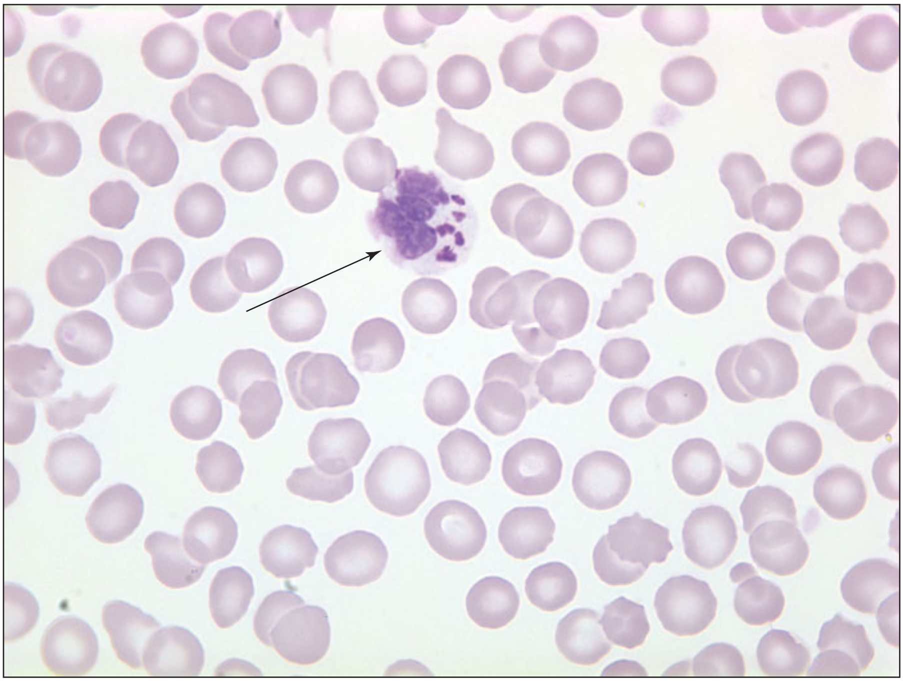


Figure **IIB1-2**

Peripheral blood smear.

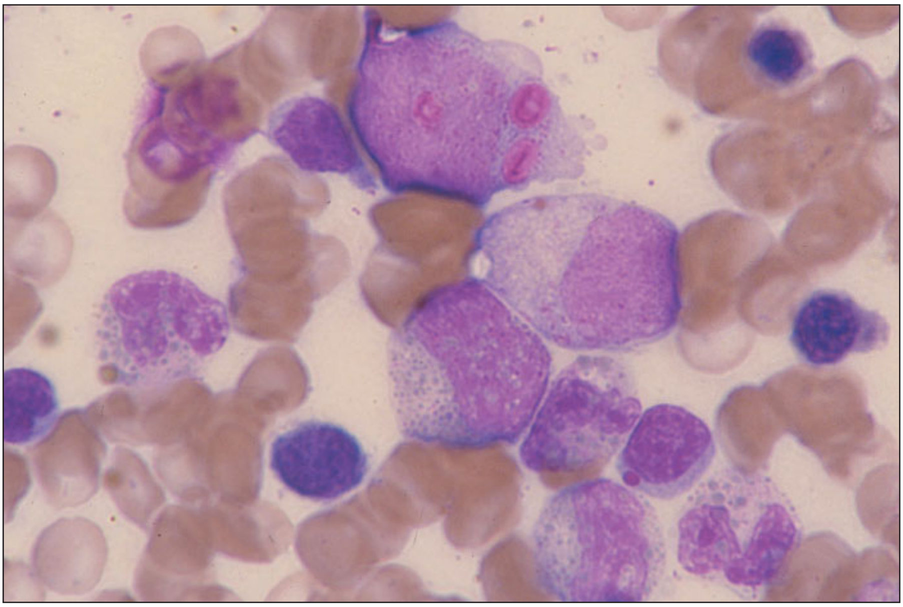


Figure **IIB1-3**

Bone marrow smear.

Clinical Features

- Increased susceptibility to bacterial infections
- Fever
- Silvery-white hair
- Photophobia
- Enlarged lymph nodes
- Hepatosplenomegaly

Pathology

- Autosomal recessive inherited disorder of granule production
- Produces serious abnormalities in the function of affected phagocytes
  - Bacterial killing is impaired
  - Degranulation is delayed and incomplete
  - Chemotaxis is defective
- Lymphocytes show an impairment of both antibody-dependent and natural killer cell–mediated cytotoxicity

Laboratory Features

White Blood Cells

- Typical count of 1–3 × 10^9/L
- Giant gray-green peroxidase-positive bodies are found in the cytoplasm of leukocytes
- Neutropenia

Red Blood Cells

- Normal

Platelets

- Thrombocytopenia
- Aggregation is abnormal

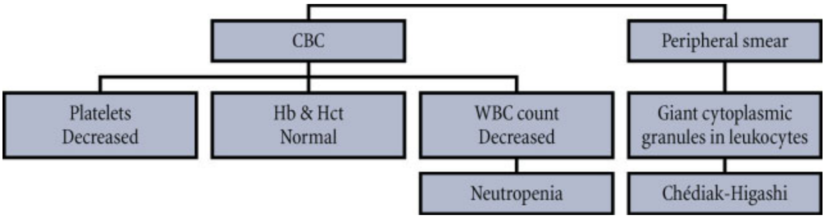
Coagulation studies

- Bleeding time is abnormal

Bone Marrow

- The abnormal granules from precursor vacuoles undergo fusion

Diagnostic Scheme


CBC
Peripheral smear
Platelets Decreased
Hb & Hct Normal
WBC count Decreased
Giant cytoplasmic granules in leukocytes
Neutropenia
Chédiak-Higashi

CHRONIC GRANULOMATOUS DISEASE

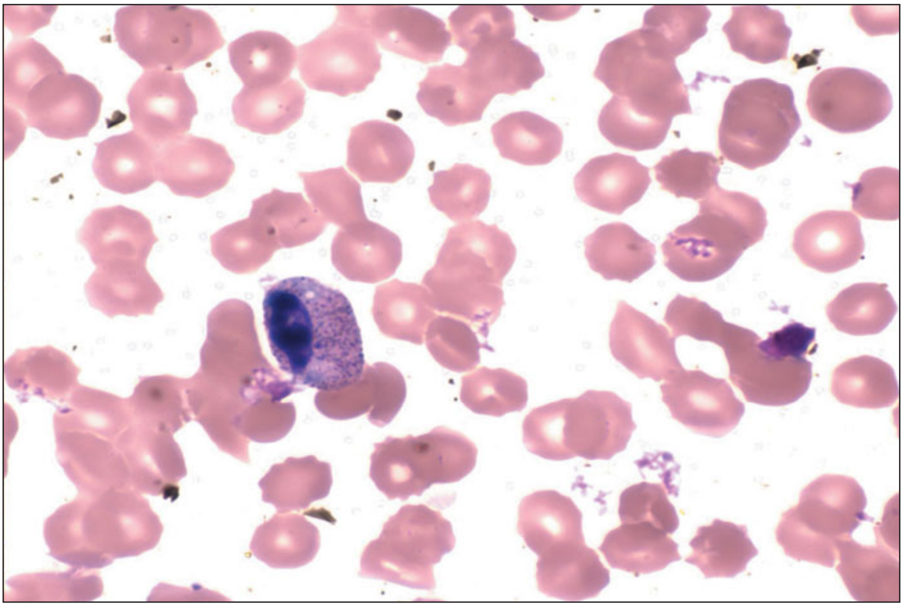


Figure IIB1-4

Nitroblue tetrazolium stain—negative.

Clinical Features

- Recurrent bacterial and fungal infections during the first 12 months of life
- Lymphadenitis
- Deep tissue infections
- Infected eczemalike rash
- Visceral and hepatic abscesses
- Recurrent pulmonary infections
- Organomegaly

Pathology

- May be inherited as an X-linked or as an autosomal recessive trait
- Failure in the activation of the respiratory burst
- Formation of granulomas during chronic inflammatory reactions

Laboratory Features

White Blood Cells

- Neutrophilia
- Nitroblue tetrazolium reduction test results negative
  - In this test, neutrophils are incubated in the presence of nitroblue tetrazolium along with an activating agent
  - The superoxide that is released reduces the dye to an insoluble dark blue formazan that can be seen as a granular precipitate in the neutrophils (see positive control)

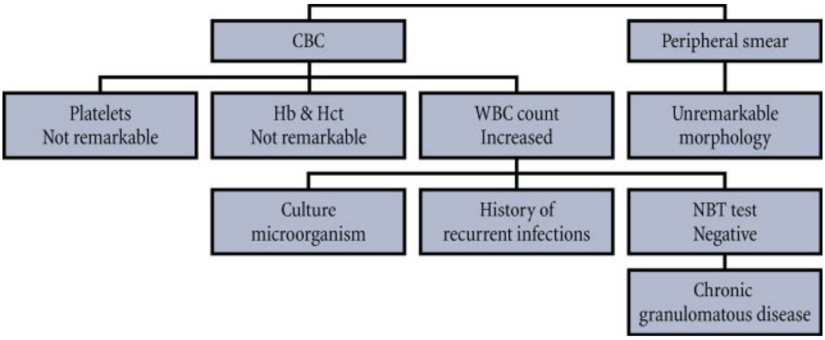
Red Blood Cells

- Not remarkable

Platelets

- Not remarkable

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Not remarkable
WBC count Increased
Unremarkable morphology
Culture microorganism
History of recurrent infections
NBT test Negative
Chronic granulomatous disease

EOSINOPHILIA

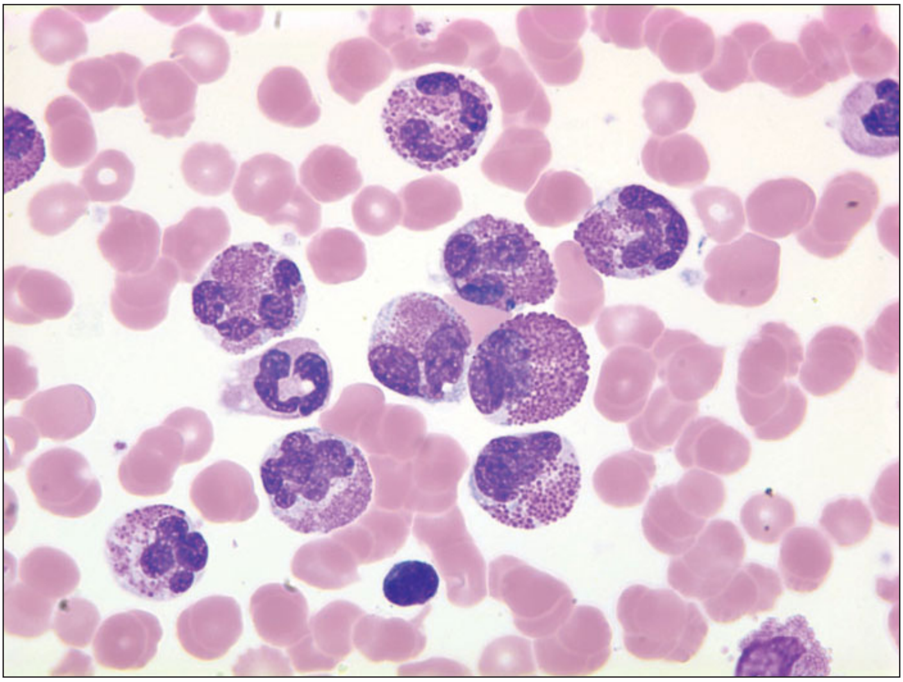


Figure IIB1-5

Peripheral blood smear.

Clinical Features

- Depends on the etiology—may see fever, skin rash, adenopathy, cough, pulmonary infiltrates, muscle pain, hepatosplenomegaly

Pathology

- Absolute eosinophil count of $>0.6 \times 10^9$/L
- Causes include:
  - Parasitic infection
  - Allergic reaction
  - Respiratory disorders
  - Neoplastic diseases
  - Inflammatory or autoimmune diseases
  - Skin disorders

Laboratory Features

White Blood Cells

- Count normal to increased
- Eosinophils increased

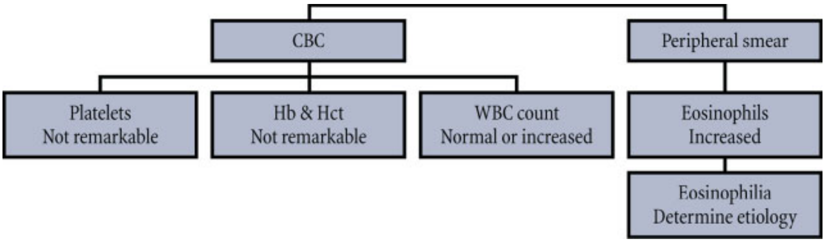
Red Blood Cells

- Not remarkable

Platelets

- Not remarkable

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Not remarkable
WBC count Normal or increased
Eosinophils Increased
Eosinophilia Determine etiology

INFECTIOUS MONONUCLEOSIS

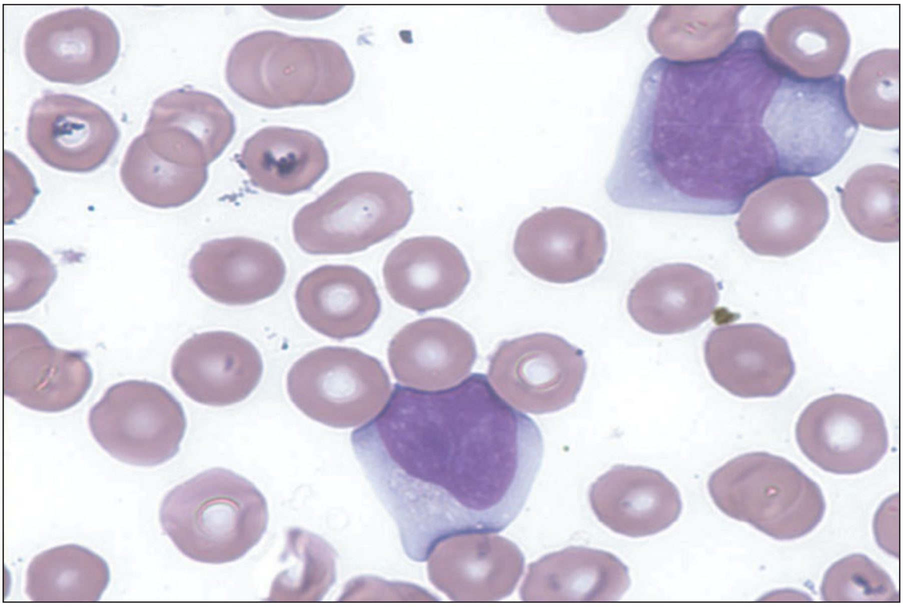


Figure IIB1-6

Peripheral blood smear.

Clinical Features

- Usually occurs in young adults aged 14–24 years
- Lethargy, anorexia, nausea, headache, chills, fever, pharyngitis, lymphadenopathy, splenomegaly, hepatomegaly
- Usually self-limited

Pathology

- Epstein-Barr virus attaches to the B lymphocytes by means of a specific Epstein-Barr virus receptor on the lymphocyte membrane
- B lymphocytes and lymphoid tissues throughout the body are involved
- Incubation period is about 30–50 days

Laboratory Features

White Blood Cells

- Agranulocytosis
- Proliferation of lymphocytes (12–25 × 10^9/L)
- >20% reactive lymphocytes
- Immunoblasts may be present
- Plasmacytoid lymphocytes may be present

Red Blood Cells

- May have an autoimmune hemolytic anemia

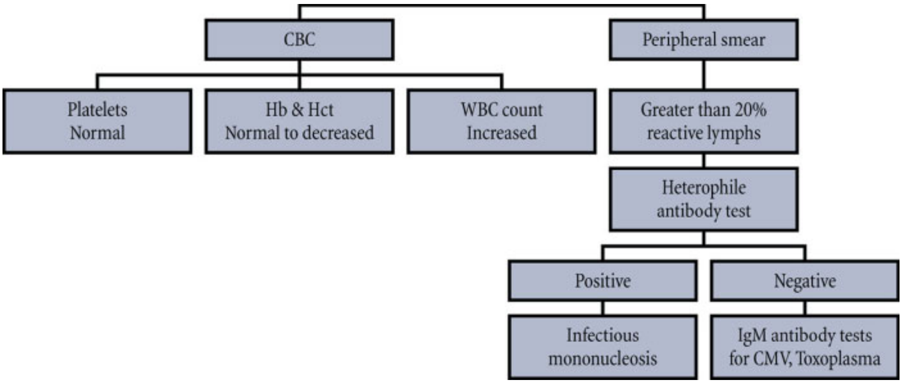
Platelets

- Normal to decreased

Serologic Tests

- Paul-Bunnell heterophile antibodies positive

Diagnostic Scheme


CBC
Peripheral smear
Platelets Normal
Hb & Hct Normal to decreased
WBC count Increased
Greater than 20% reactive lymphs
Heterophile antibody test
Positive
Negative
Infectious mononucleosis
IgM antibody tests for CMV, Toxoplasma

LYMPHOCYTOSIS

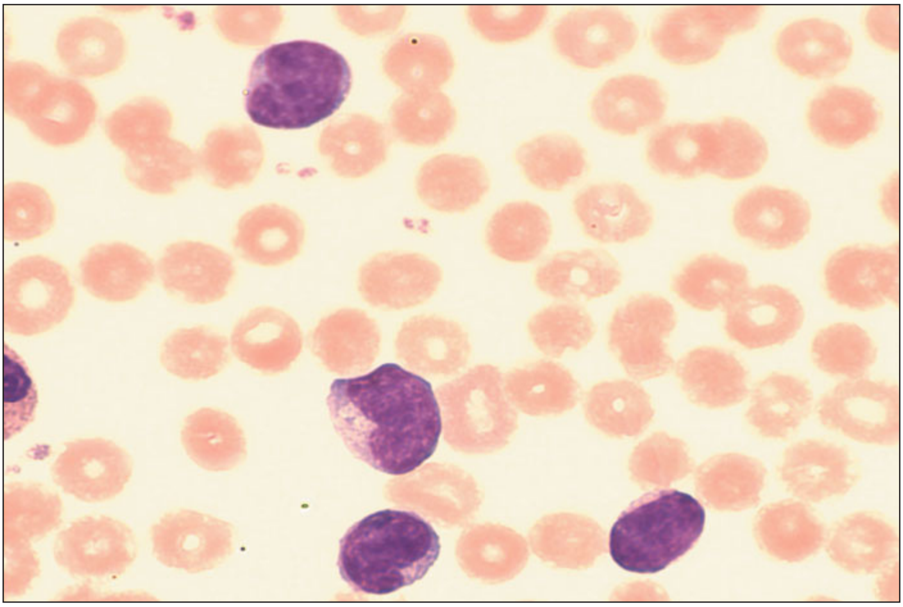


Figure IIB1-7

Peripheral blood smear—whooping cough.

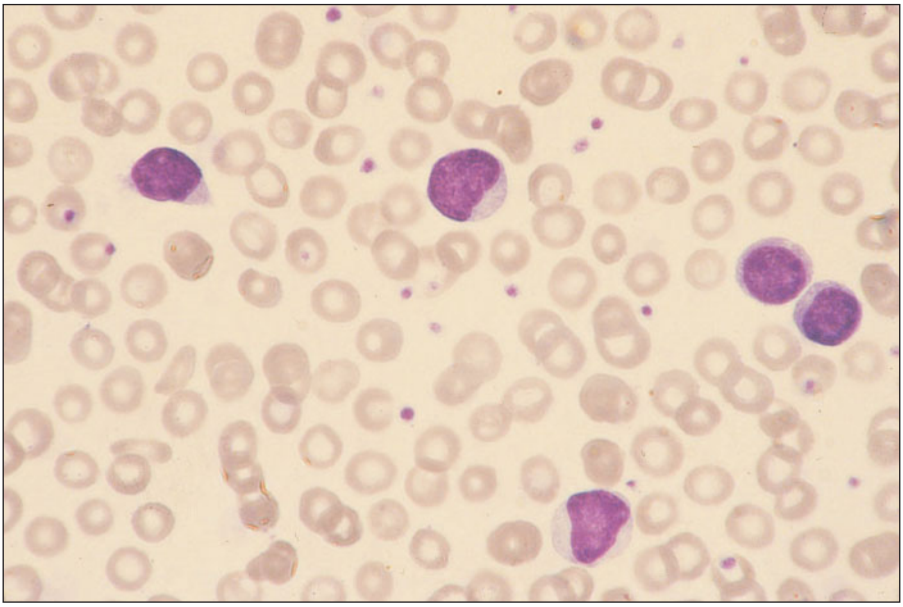


Figure IIB1-8

Peripheral blood smear—infectious lymphocytosis.

Clinical Features

- Benign conditions
  - Viral infections
  - Bacterial infections
  - Protozoal infections
  - Other
- Malignant conditions

Bacterial Infections

- Incubation period is about 2 weeks
- Head cold, paroxysmal cough, pain in the neck and chest

Protozoal Infections (Toxoplasmosis)

- Congenital—hepatosplenomegaly, jaundice, microcephaly, mental retardation
- Acquired—lethargy, anorexia, nausea, headache, chills and fever, pharyngitis, lymphadenopathy to asymptomatic

Viral Infections (Cytomegalovirus)

- Congenital—only 10% of infected newborns show the clinical features, which include microcephaly, hepatosplenomegaly, and jaundice
- Acquired—lethargy, anorexia, nausea, headache, chills, fever, lymphadenopathy, splenomegaly, hepatomegaly

Infectious Lymphocytosis

- Usually affects young children aged 1–10 years
- Occurs in epidemics
- Incubation time is about 2–3 weeks
- Usually asymptomatic

Pathology

Bacterial Infections

- *Bordetella pertussis* infection (whooping cough)
- Usually in nonimmunized children

Protozoal Infections

- Usually the result of infection by *Toxoplasma gondii*
- Multiply in all body cells except red blood cells
- Congenital—results from placental transmission from parasitized mother
- Acquired—ingestion of oocyts from undercooked meat or inhalation from cat feces

Viral Infections

- Commonly from the cytomegalovirus
- Virus infects leukocytes, which transport it to other locations
- Virus suppresses cell-mediated immune function
- Congenital—transplacental transmission from an infected mother
- Acquired—may be spread by close contact or by blood transfusion

Infectious Lymphocytosis

- Caused by a virus, probably of the Coxsackie group
- Usually affects children younger than 10 years
- Usually no symptoms

Laboratory Features

Bacterial Infections

White Blood Cells

- Increased lymphocyte count (up to 15–56 × 10^9/L)

Red Blood Cells

- Not remarkable

Platelets

- Not remarkable

Protozoal Infections

White Blood Cells

- Increased
- Lymphocytosis with the presence of reactive lymphocytes
- Eosinophilia may be present

Red Blood Cells

- Hemolytic anemia

Platelets

- Variable

Serologic Tests

- Heterophile antibody test result negative

Viral Infections

White Blood Cells

- Increased
- Lymphocytosis with the presence of reactive lymphocytes

Red Blood Cells

- Hemolytic anemia

Platelets

- Variable

Serologic Tests

- Heterophile antibody test result negative

Infectious Lymphocytosis

White Blood Cells

- Usually 20.0–30.0 × 10^9/L
- 50–95% normal-appearing, small lymphocytes

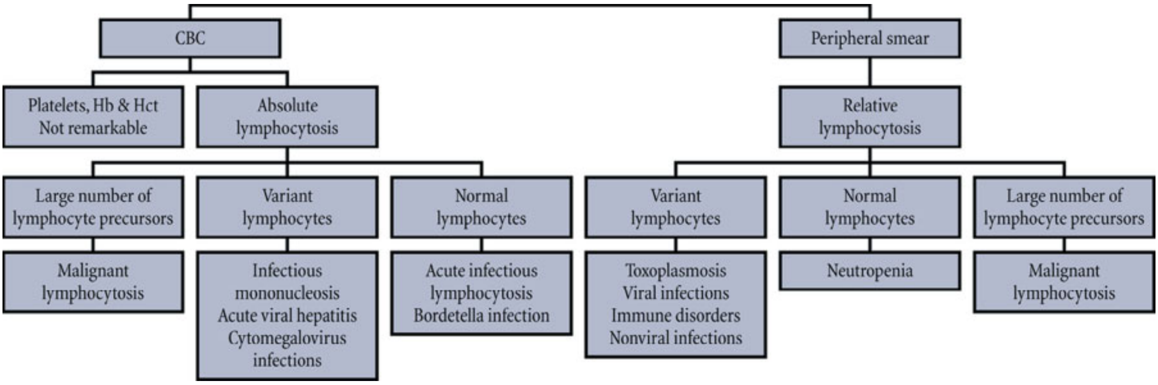
Red Blood Cells

- Not remarkable

Platelets

- Not remarkable

Diagnostic Scheme


CBC
Peripheral smear
Platelets, Hb & Hct Not remarkable
Absolute lymphocytosis
Relative lymphocytosis
Large number of lymphocyte precursors
Variant lymphocytes
Normal lymphocytes
Variant lymphocytes
Normal lymphocytes
Large number of lymphocyte precursors
Malignant lymphocytosis
Infectious mononucleosis
Acute viral hepatitis
Cytomegalovirus infections
Acute infectious lymphocytosis
Bordetella infection
Toxoplasmosis
Viral infections
Immune disorders
Nonviral infections
Neutropenia
Malignant lymphocytosis

MAY-HEGGLIN ANOMALY

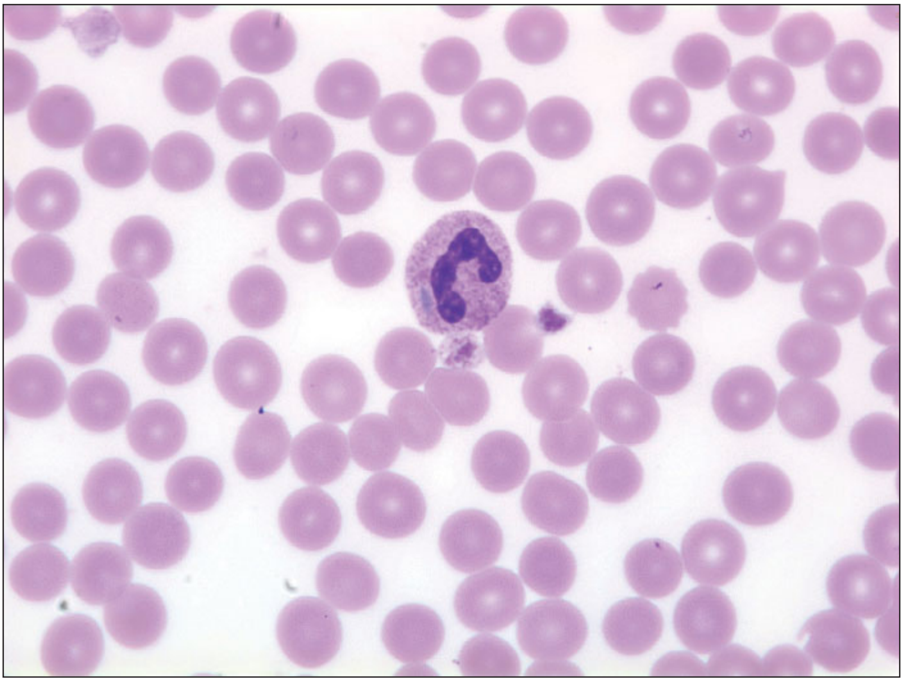


Figure IIB1-9

Peripheral blood smear.

Clinical Features

- Usually a mild bleeding disorder—epistaxis, bruising, gingival bleeding, dysmenorrhea, and abnormal bleeding after dental extractions or surgery

Pathology

- Inherited as an autosomal dominant trait affecting white blood cells and platelets

Laboratory Features

White Blood Cells

- Most neutrophils contain small homogeneous blue inclusions
- Inclusions are larger than Döhle bodies, spindle or crescent shaped, and light blue
- Found in neutrophils, eosinophils, basophils, monocytes, and occasionally even lymphocytes

Red Blood Cells

- Normal

Platelets

- Giant platelets
- Mean platelet volume increased
- Number decreased

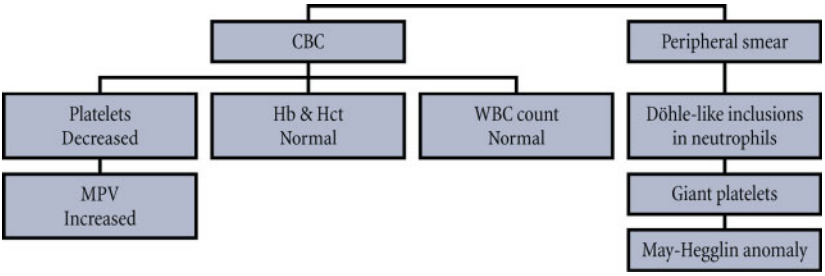
Coagulation Studies

- Bleeding time is prolonged

Bone Marrow

- Number of megakaryocytes is normal but show some large hypergranular platelets in the cytoplasm

Diagnostic Scheme


CBC
Peripheral smear
Platelets Decreased
Hb & Hct Normal
WBC count Normal
Döhle-like inclusions in neutrophils
MPV Increased
Giant platelets
May-Hegglin anomaly

MONOCYTOSIS

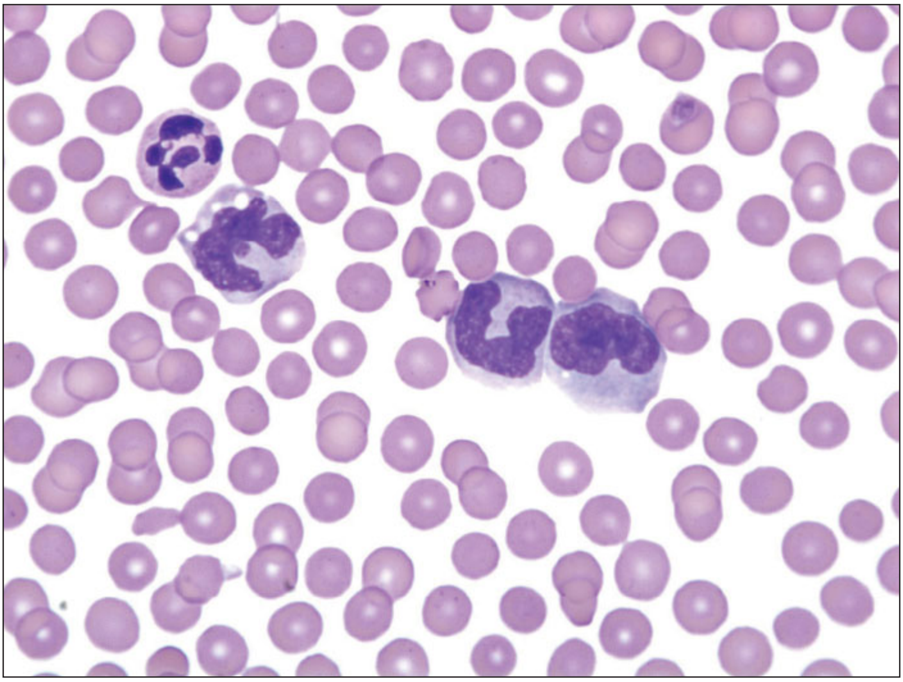


Figure IIB1-10

Peripheral blood smear.

Clinical Features

- In adults, defined as >0.95 × 10^9/L monocytes
- In infants and children, defined as >1.0 × 10^9/L monocytes
- Causes of neutrophilia may be accompanied by absolute monocytosis
- Relative monocytosis may indicate a recovery from agranulocytosis or marrow hypoplasia

Pathology

- Monocytes play a role in inflammation and immune reactions
- Monocytosis is associated with several conditions
  - Tuberculosis
  - Malignancies
  - Myelodysplastic syndromes
  - Myeloproliferative neoplasms
  - Lymphocytic tumors
  - Inflammatory disorders

Laboratory Features

White Blood Cells

- Increased monocytes

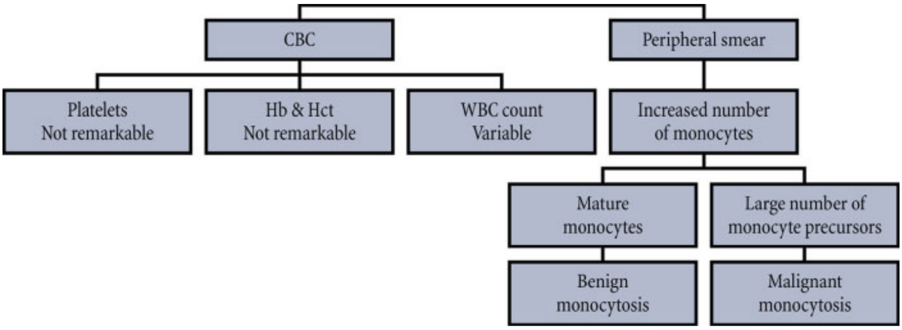
Red Blood Cells

- Not remarkable

Platelets

- Not remarkable

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Not remarkable
WBC count Variable
Increased number of monocytes
Mature monocytes
Large number of monocyte precursors
Benign monocytosis
Malignant monocytosis

NEUTROPENIA

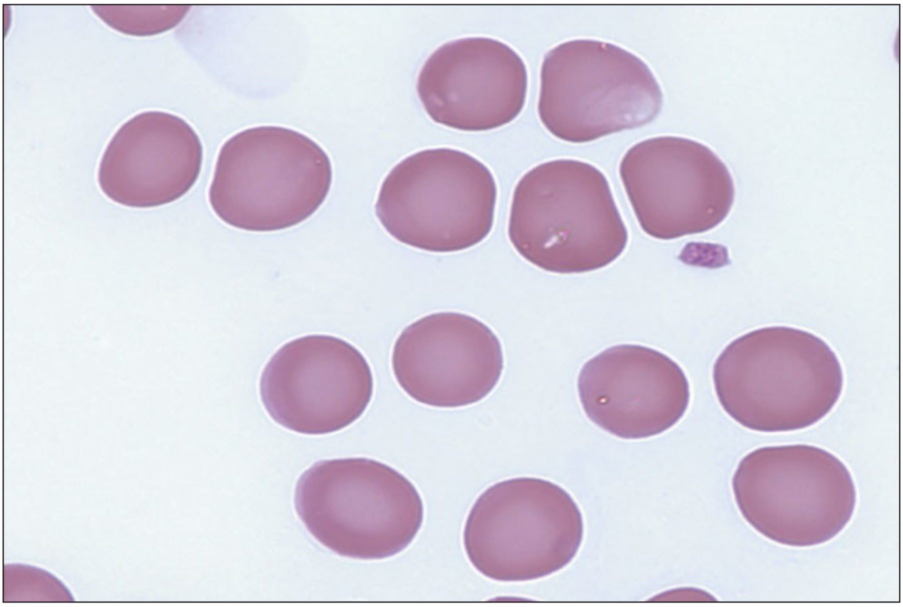


Figure IIB1-11

Peripheral blood smear.

Clinical Features

- Defined as an absolute neutrophil count of $<1.5 \times 10^9$/L
- May have no symptoms or may present with sudden overwhelming sepsis
  - Fever
  - Enlarged lymph nodes
  - Sternal tenderness
  - Oral lesions
- Hepatosplenomegaly

Pathology

- Decreased or ineffective production
- Reduced survival
- Abnormal distribution and sequestration

Laboratory Features

White Blood Cells

- Total number decreased
- Neutrophil count decreased

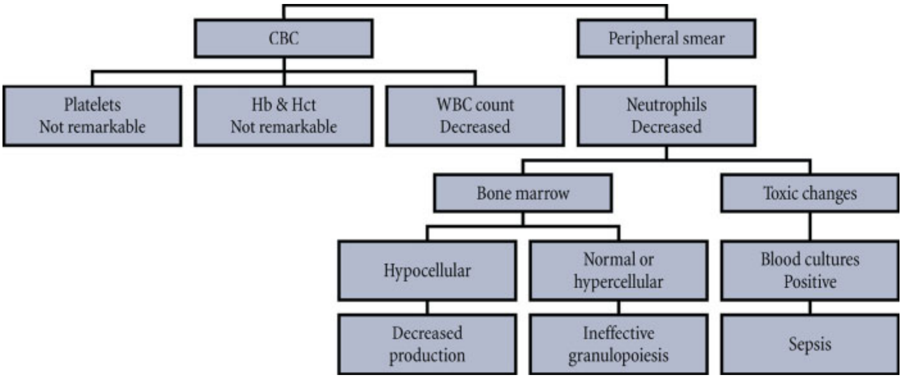
Red Blood Cells

- Not remarkable

Platelets

- Not remarkable

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Not remarkable
WBC count Decreased
Neutrophils Decreased
Bone marrow
Toxic changes
Hypocellular
Normal or hypercellular
Blood cultures Positive
Decreased production
Ineffective granulopoiesis
Sepsis

NEUTROPHILIA

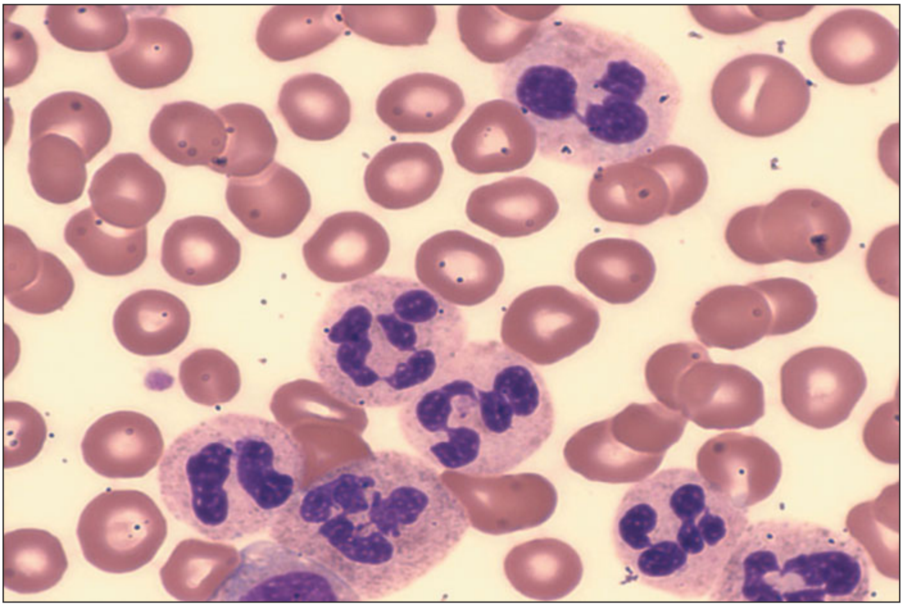


Figure IIB1-12

Peripheral blood smear.

Clinical Features

- Defined as an absolute count of >7.0 × 10^9/L
- Acute neutrophilia may be caused by exercise, stress, drugs, and hormones, and the most frequent cause is bacterial infection
- Chronic neutrophilia may be seen with infection, chronic inflammation, tumors, or hematologic disorders

Pathology

- Increased production by the bone marrow
- Increased release from the marrow reserve or impaired egress from the peripheral blood
- Decreased neutrophil count in the marginating pool, with increased neutrophil count in the circulating pool
- Extreme neutrophilic reactions to severe infections or necrotizing tissue may produce a leukemoid reaction (usually >50.0 × 10^9/L)
- Neoplastic disorders

Laboratory Features

White Blood Cells

- Physiologic neutrophilia
  - Increased count
- Pathologic neutrophilia
  - Increased count
  - Shift to the left
  - Vacuolization and toxic granulation
  - Döhle bodies

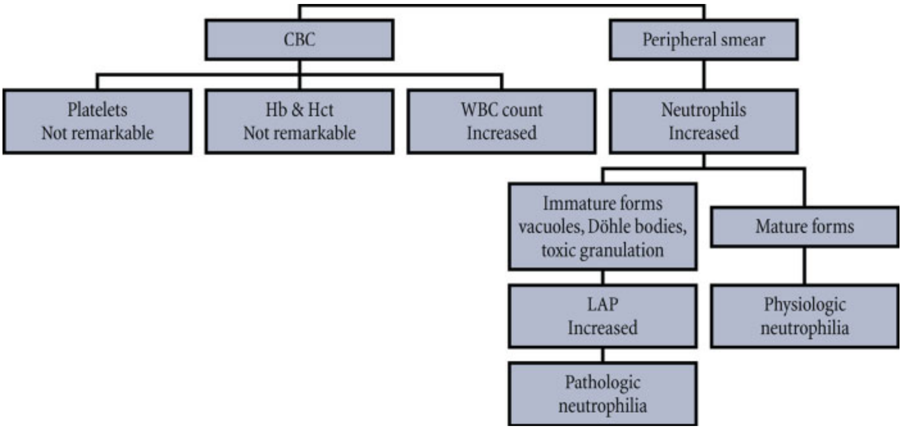
Red Blood Cells

- Not remarkable

Platelets

- Not remarkable

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Not remarkable
WBC count Increased
Neutrophils Increased
Immature forms vacuoles, Döhle bodies, toxic granulation
Mature forms
LAP Increased
Physiologic neutrophilia
Pathologic neutrophilia

PELGER-HUËT ANOMALY

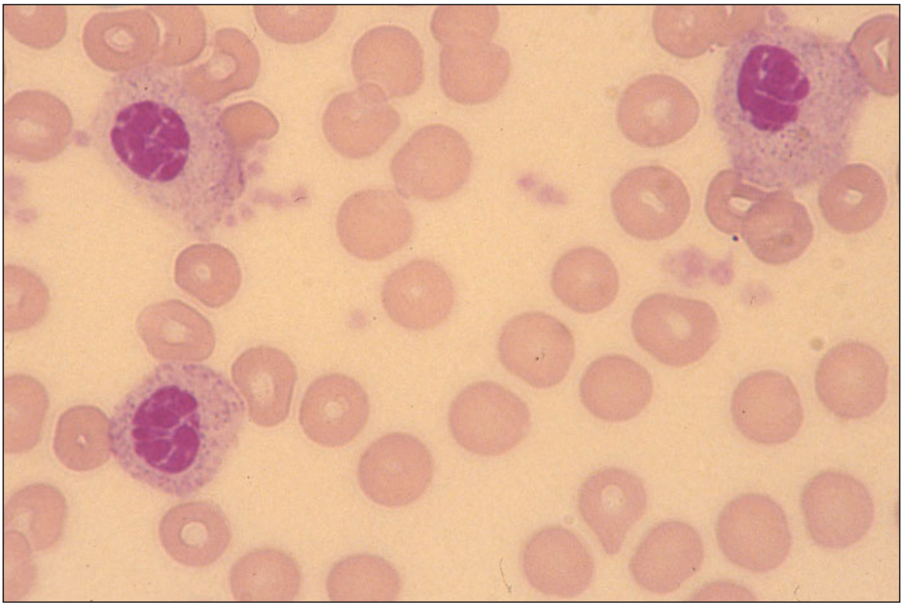


Figure IIB1-13

Peripheral blood smear—homozygous.

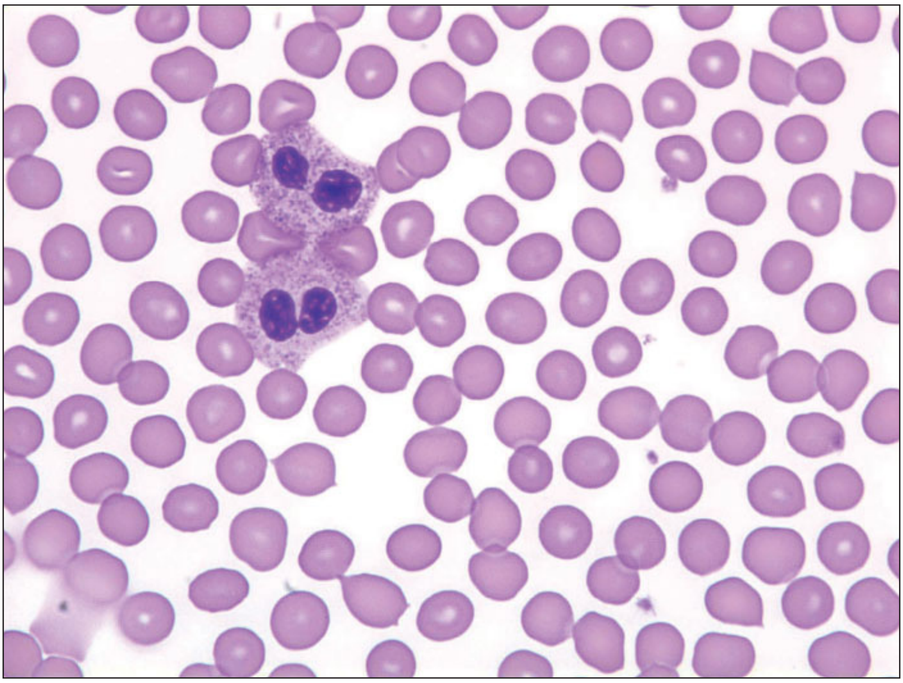


Figure IIB1-14

Peripheral blood smear—heterozygous.

Clinical Features

- No clinical significance is associated with this anomaly

Pathology

- Inherited as an autosomal dominant trait
- Decreased segmentation of the nucleus of granulocytes
- Marked condensation of nuclear chromatin
- Normal cytoplasmic maturation

Laboratory Features

White Blood Cells

- In the heterozygous state, the granulocyte nucleus is bilobed or dumbbell shaped (Pince-Nez)
- In the homozygous state, the nucleus is round or oval (Stodtmeister)

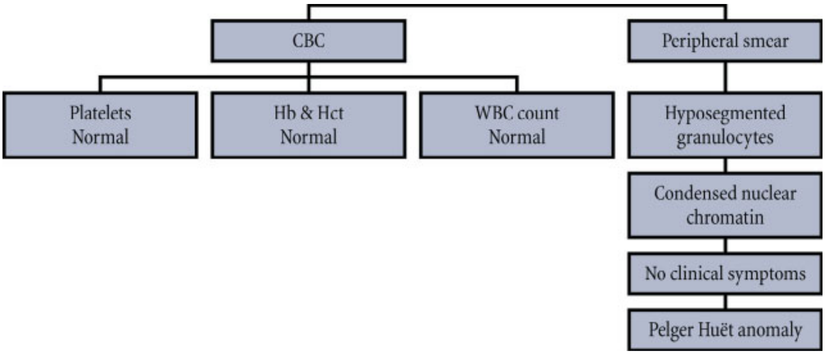
Red Blood Cells

- Not remarkable

Platelets

- Not remarkable

Diagnostic Scheme


CBC
Peripheral smear
Platelets Normal
Hb & Hct Normal
WBC count Normal
Hyposegmented granulocytes
Condensed nuclear chromatin
No clinical symptoms
Pelger Huët anomaly

CHAPTER 2

French American British (FAB) Classification of Leukemia

FAB CLASSIFICATION OF LEUKEMIAS

Background

- Organized in 1976 in an attempt to provide a uniform means of discussing the leukemias worldwide. The classifications were based on morphology and cytochemistry

Definitions

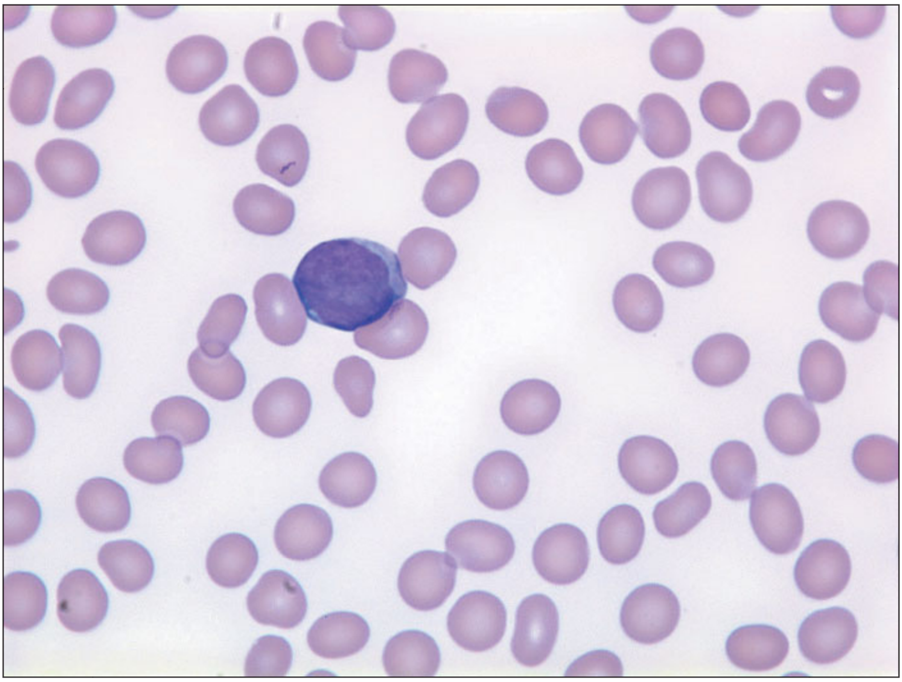


Figure IIB2-1

Peripheral blood smear.

Type I Blast—Indistinguishable from Normal Myeloblasts

Nucleus

- Immature with uncondensed chromatin pattern, centrally positioned

Cytoplasm

- Granules always absent

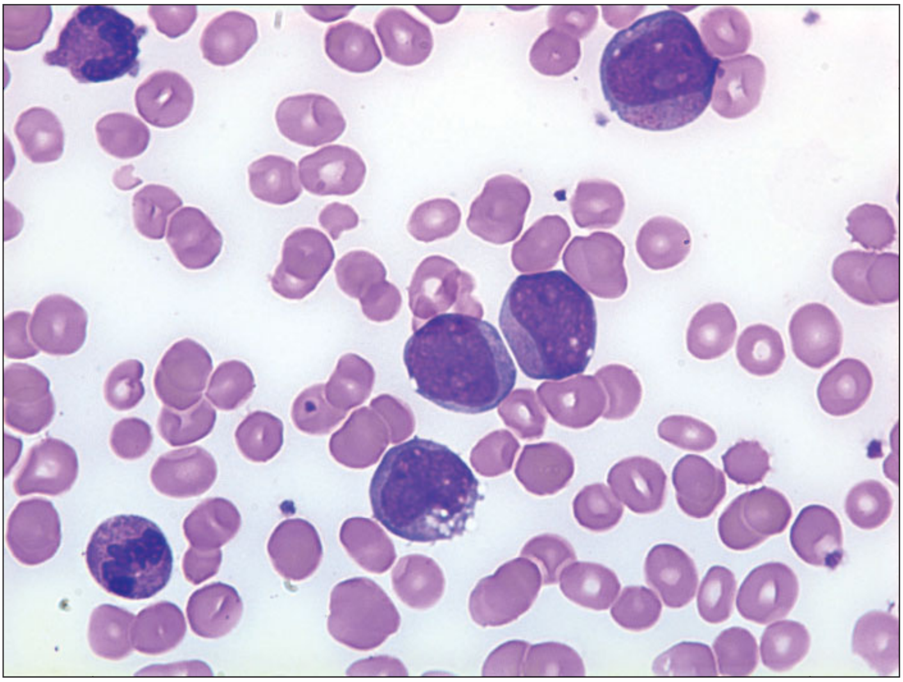


Figure IIB2-2

Peripheral blood smear.

Type II Blast—Resembles Type I Blasts

Nucleus

- Centrally positioned
- N/C ratio is slightly lower than Type I

Cytoplasm

- Few primary granules but <20

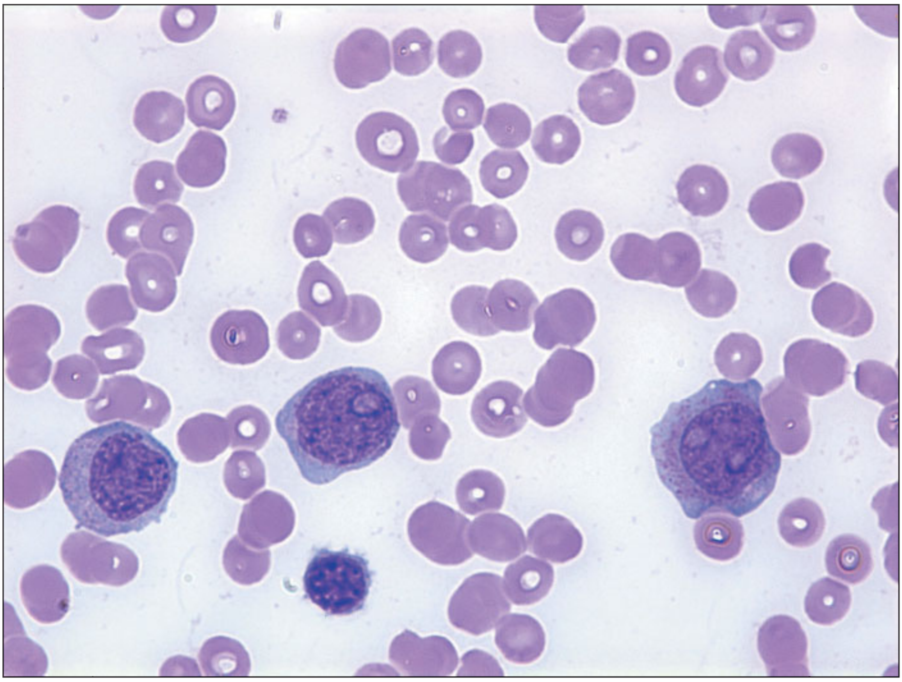


Figure IIB2-3

Peripheral blood smear.

Type III Blast—Resembles Type II Blasts

Nucleus

- Slightly lower N/C ratio

Cytoplasm

- >20 granules but granules do not obscure the nucleus

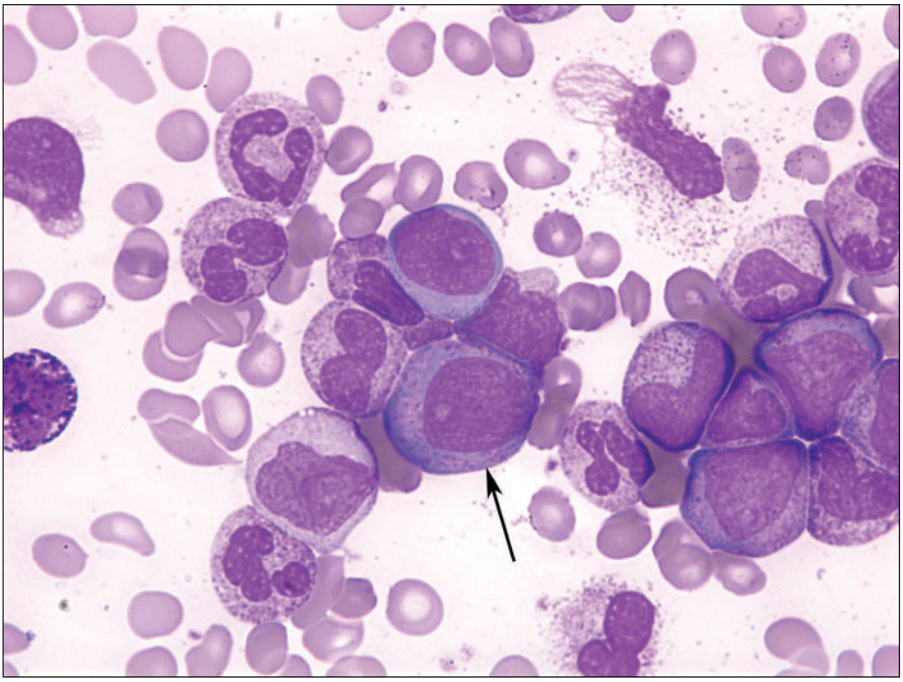


Figure **IIB2-4**

Peripheral blood smear.

Promyelocyte

Nucleus

- Eccentric, chromatin is condensed
- Low N/C ratio

Cytoplasm

- Numerous azurophilic granules which obscure the nucleus

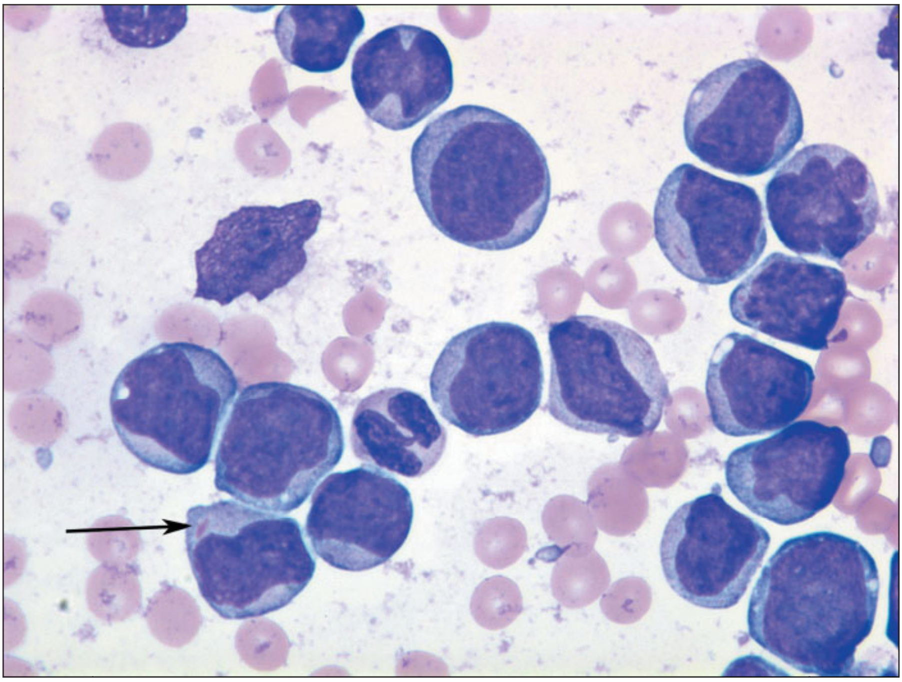


Figure **IIB2-5**

Bone marrow smear.

Auer Rod

- The fusion of primary granules forming a spindle- or rod-shaped inclusion

Peripheral Blood Findings

- 90% of patients have moderate-to-severe neutropenia
- 50% of patients have a leukocytosis
- 30% of patients have a leukopenia
- The blasts are of variable size
- 70–80% of the patients have normochromic, normocytic anemia
- 60% of the patients have hematocrits of <30%
- Thrombocytopenia is usually present

Bone Marrow Findings

- A blast count of >30% is diagnostic of acute leukemia

Cytochemistry

- Type I, II, and III myeloblasts show 3% positivity of blasts for peroxidase (MPO), Sudan black B (SBB), or specific esterase
- Monoblasts and promonocytes are positive with nonspecific esterase
- Erythroblasts and megakaryoblasts are positive with PAS

FAB CLASSIFICATION M0–M7

M0 (Acute Myeloid Leukemia with Minimal Differentiation)

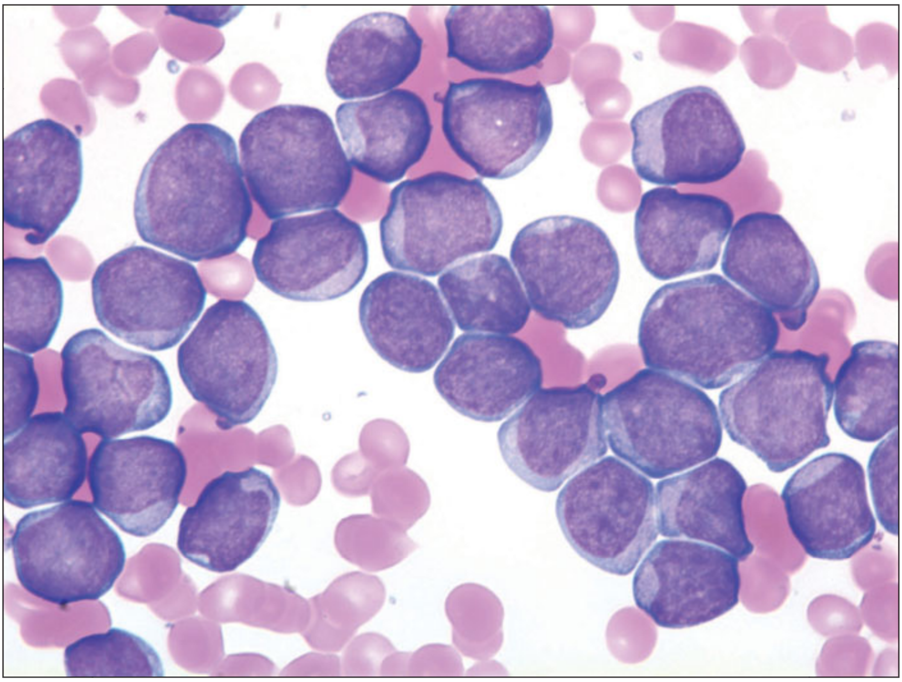


Figure IIB2-6

Peripheral blood smear.

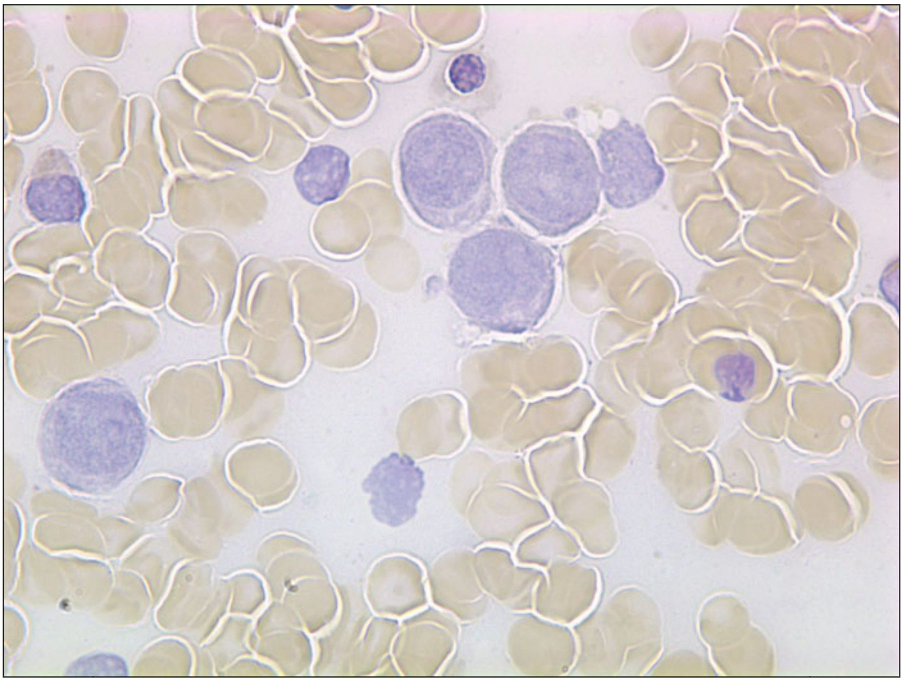


Figure IIB2-7

Sudan black B stain.

Criteria

Peripheral Blood

- Blasts are agranular
- Platelets are decreased

Bone Marrow

- >30% blasts
- >20% blasts are reactive for myeloid associated antigen
- Myeloblasts are Type I
- No Auer rods
- Blasts are negative for lymphoid associated antigens

Cytochemistry

- <3% blasts are myeloperoxidase; Sudan black B and specific esterase (chloroacetate) are positive

M1 (Acute Myeloid Leukemia Without Maturation)

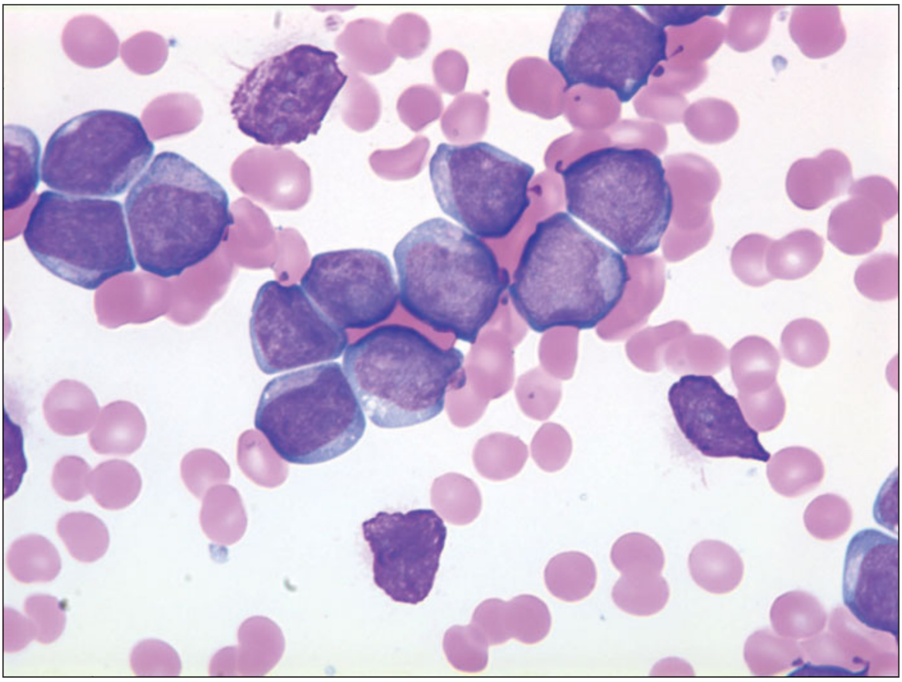


Figure **IIB2-8**

Peripheral blood smear.

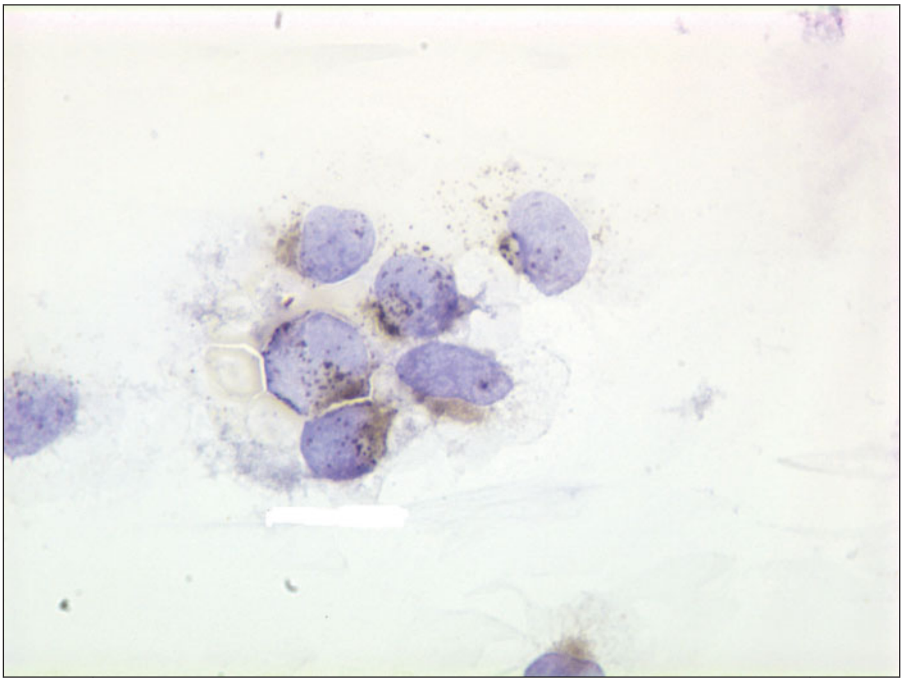


Figure **IIB2-9**

Sudan black B stain.

Criteria

Peripheral Blood

- The predominant cell is usually a Type I myeloblast
- Auer rods are rare

Bone Marrow

- >30% blasts
- 90% or more of the nonerythroid cells are myeloblasts
- <10% promyelocytes or more mature cells and monocytes

Cytochemistry

- Myeloperoxidase and Sudan black B stains are positive in more than 3% of the blasts
- Naphthol AS-D chloroacetate (specific esterase) may be positive
- Nonspecific esterases are negative

M2 (Acute Myeloid Leukemia With Maturation)

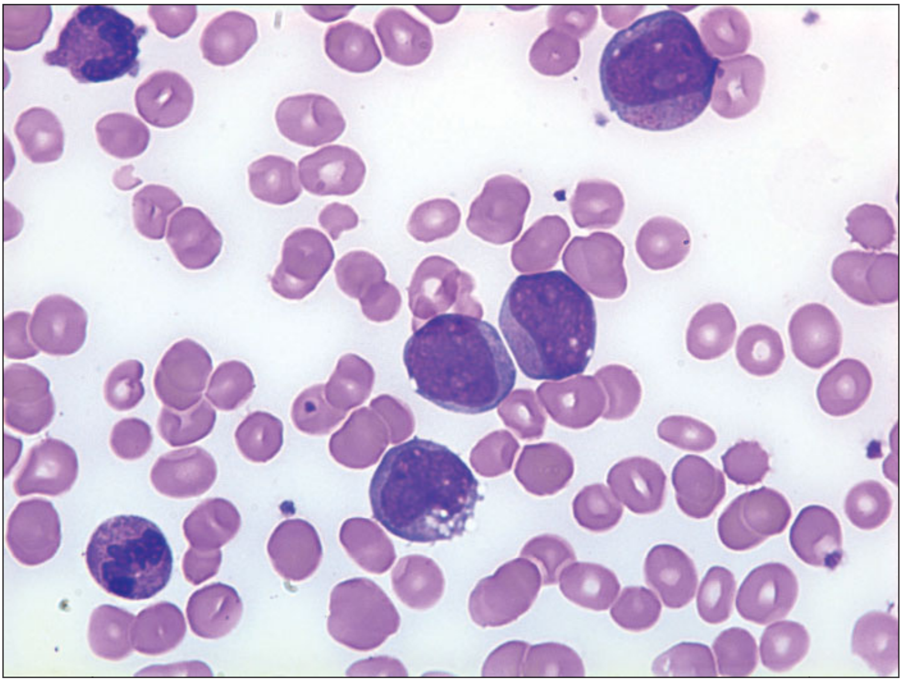


Figure IIB2-10

Peripheral blood smear.

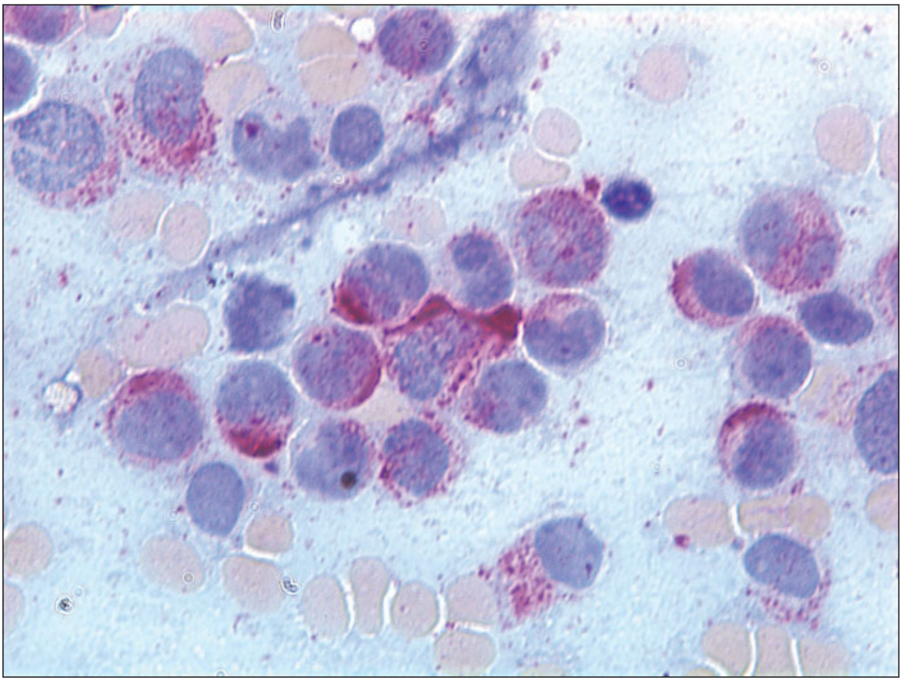


Figure IIB2-11

Specific esterase stain.

Criteria

Peripheral Blood

- Type II myeloblasts may be the predominant cell
- Auer rods typically present

Bone Marrow

- >30% blasts
- 30–89% or more of the nonerythroid cells are myeloblasts
- >10% are promyelocytes or more mature granulocytes
- Blasts are predominantly Type II or Type III

Cytochemistry

- >3% blasts are myeloperoxidase and Sudan black B positive
- Naphthol AS-D chloroacetate (specific esterase) positive

M3 (Acute Promyelocytic Leukemia–Hypergranular)

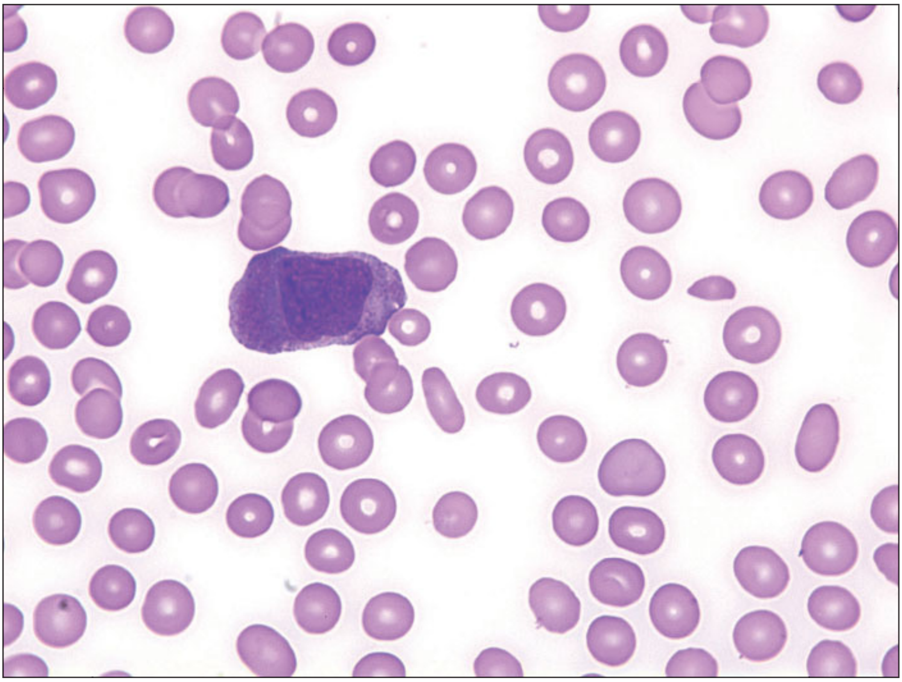


Figure IIB2-12

Peripheral blood smear.

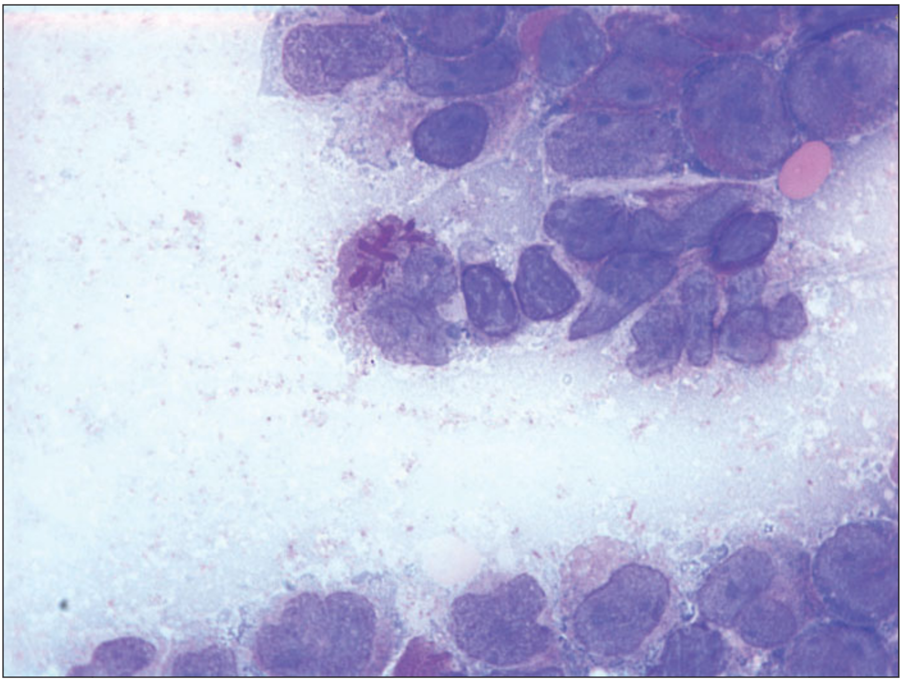


Figure IIB2-13

Bone marrow smear.

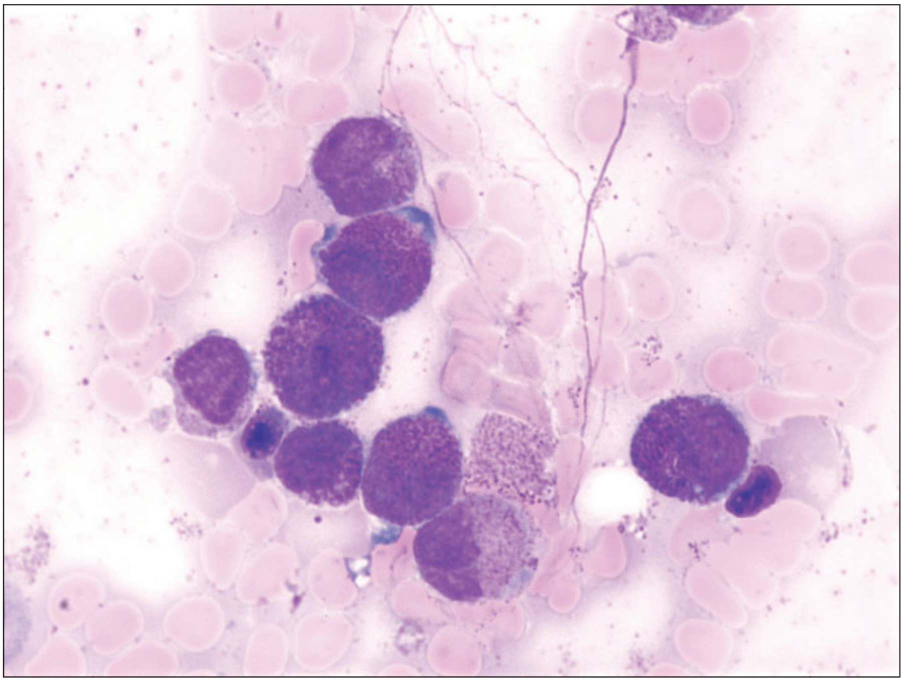


Figure **IIB2-14**

Bone marrow smear.

Criteria

- 70–80% of cases are hypergranular

Peripheral Blood

- Blasts and promyelocytes show heavy granulation and multiple Auer rods
- White blood cell count is usually decreased usually <5,000 but the range is 3,000–15,000
- Auer rods range from 10 to 20 per cell (faggot cells) and the rods may be intertwined or single. Fewer Auer rods are possible.

Bone Marrow

- Most of the cells are abnormal promyelocytes with heavy azurophilic granulation
- Multiple Auer rods found in promyelocytes (faggot cells)

M3v (Acute Promyelocytic Leukemia–Microgranular Variant)

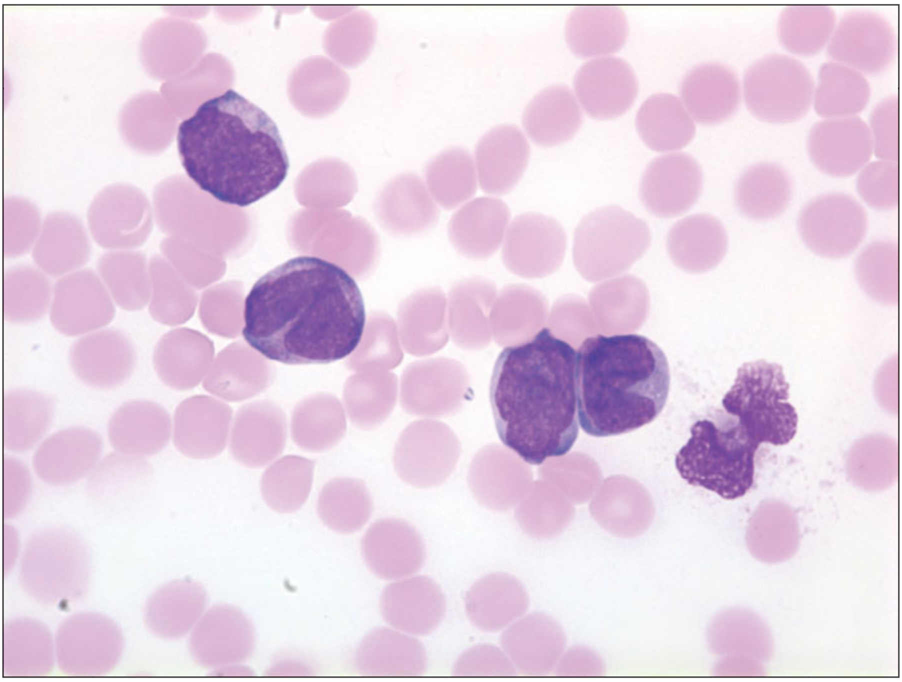


Figure IIB2-15

Peripheral blood smear.

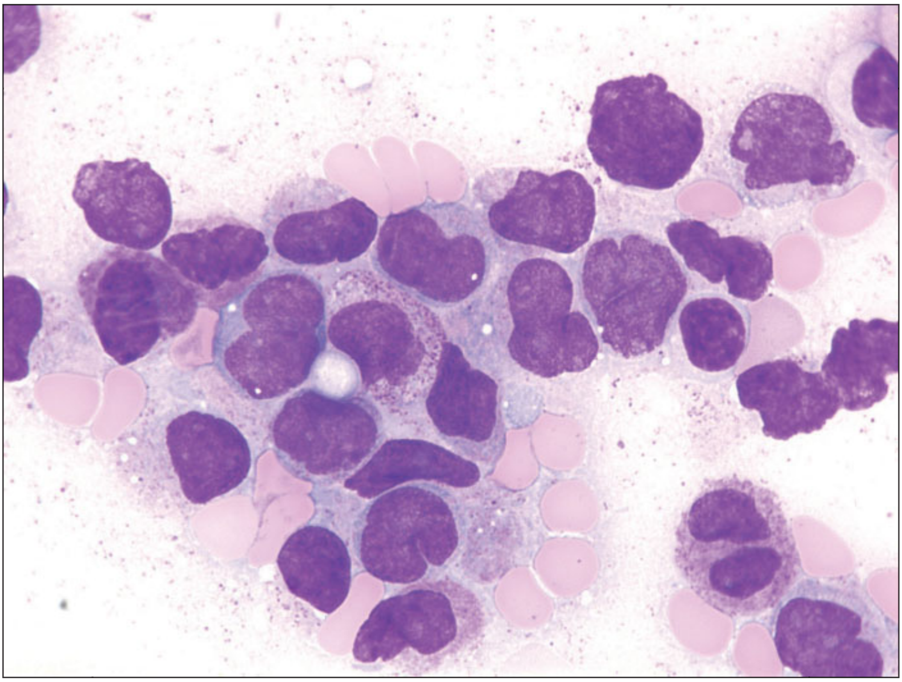


Figure IIB2-16

Bone marrow smear.

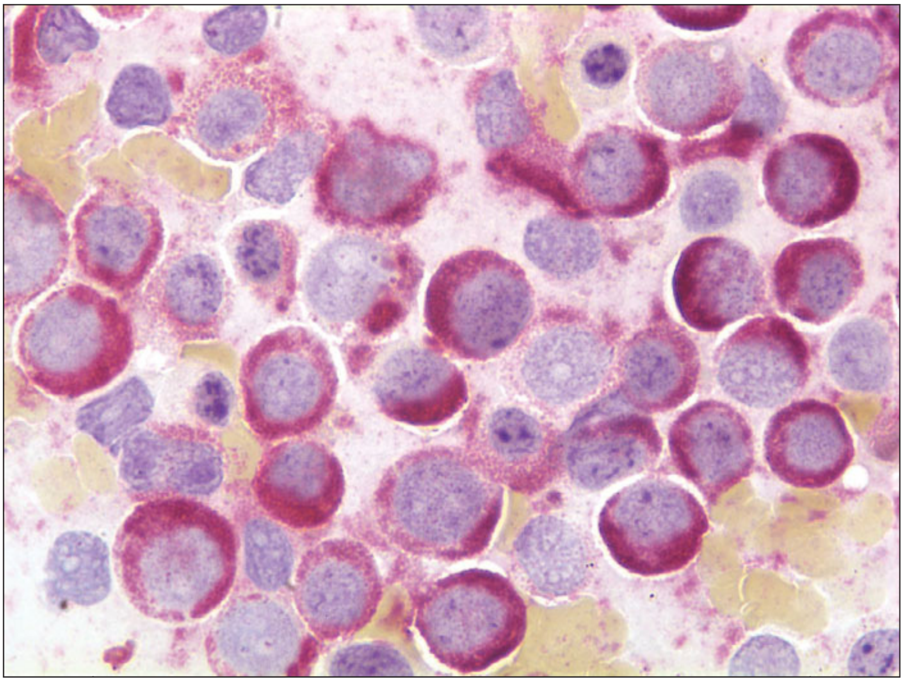


Figure **IIB2-17**

Specific esterase stain.

Criteria

- 20–30% of cases are microgranular

Peripheral Blood

- White blood cells are markedly increased
- Promyelocytes are usually bilobed and the cytoplasm contains only a few granules

Bone Marrow

- Azurophilic granules are small and difficult to see with light microscopy (<250 nm)
- Promyelocytes are large with a lower N/C ratio
- The nucleus is usually lobulated, irregular, folded, bilobed, or monocytoid in appearance

Cytochemistry

- Myeloperoxidase, Sudan black B, specific esterase positive

M4 (Acute Myelomonocytic Leukemia)

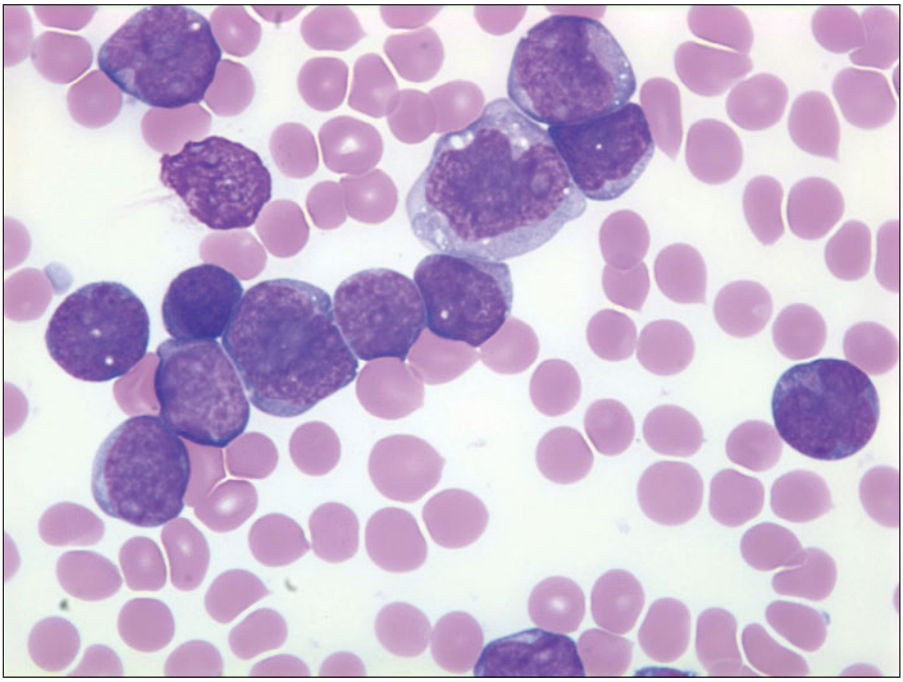


Figure IIB2-18

Peripheral blood smear.

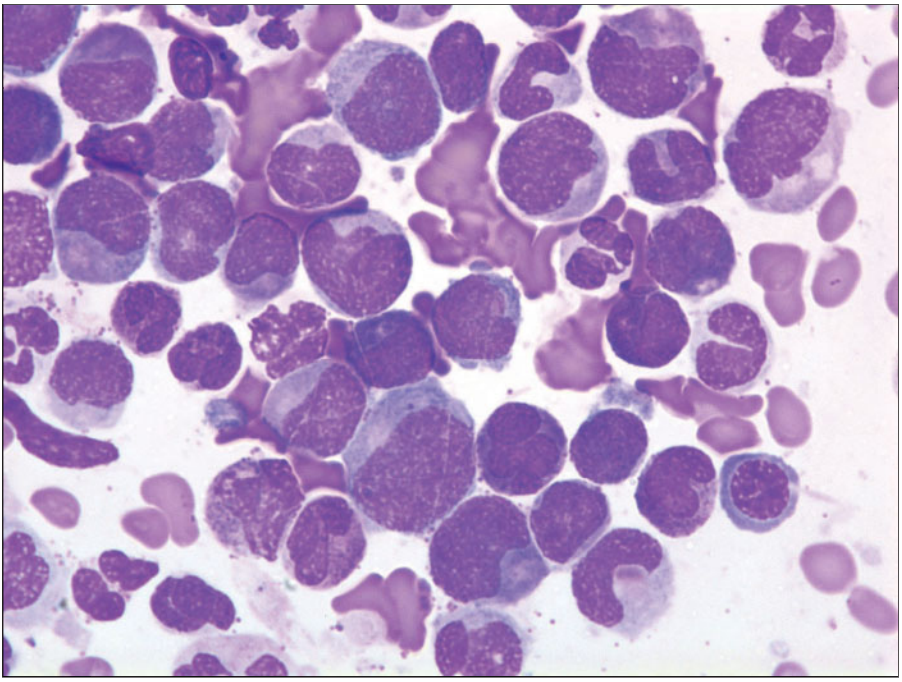


Figure IIB2-19

Bone marrow smear.

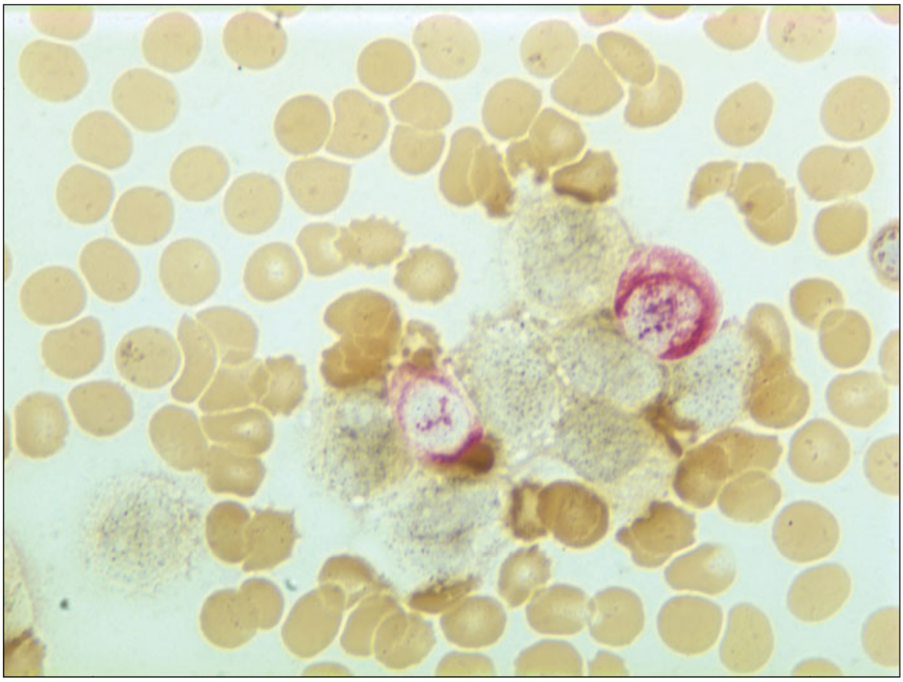


Figure **IIB2-20**

Combined esterase stain.

Criteria

Peripheral Blood

- White count is usually increased
- Both myelocytic and monocytic differentiation are found
- $>5 \times 10^9$/L monocytes and precursors are found
- Auer rods may be present

Bone Marrow

- >30% myeloblasts, monoblasts, and promonocytes
- >20% granulocytic precursors
- >20% monocytic precursors
- If the bone marrow has <20% monocytic component, then it must have a peripheral blood monocytosis of $>5 \times 10^9$/L (monocytes and precursors)
- Blast percentage includes Type I and Type II myeloblasts, monoblasts, and promonocytes

Cytochemistry

- Myeloblasts are positive for myeloperoxidase, Sudan black B, and specific esterase and negative with nonspecific esterases
- Monoblasts and promonocytes are negative or only slightly positive myeloperoxidase and negative or only finely granular with Sudan black B
- Nonspecific esterase is positive and inhibited by sodium fluoride

M4eo (Acute Myelomonocytic Leukemia with Increased Bone Marrow Eosinophils)

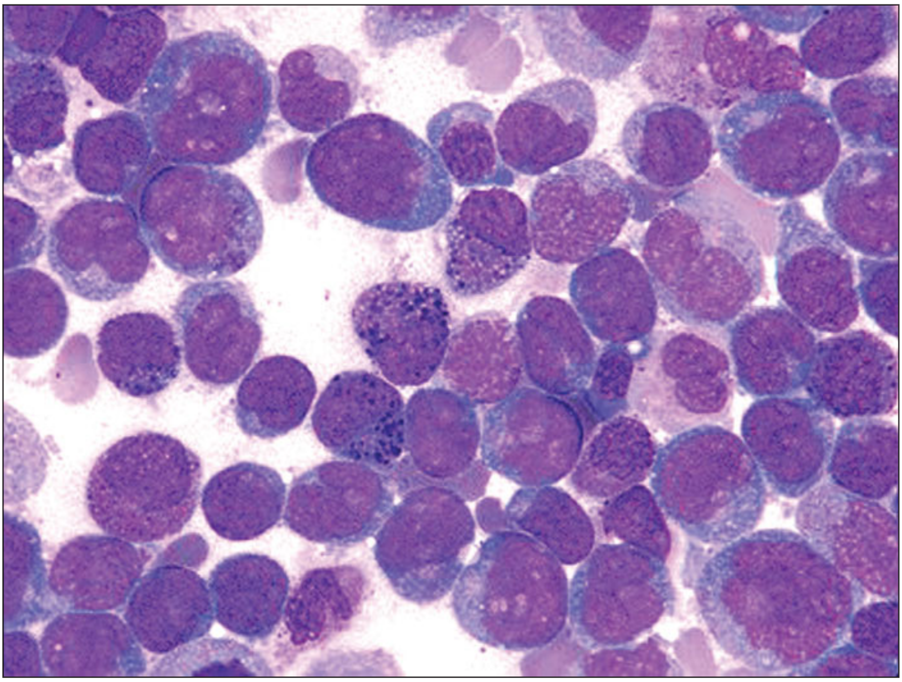


Figure IIB2-21

Bone marrow smear.

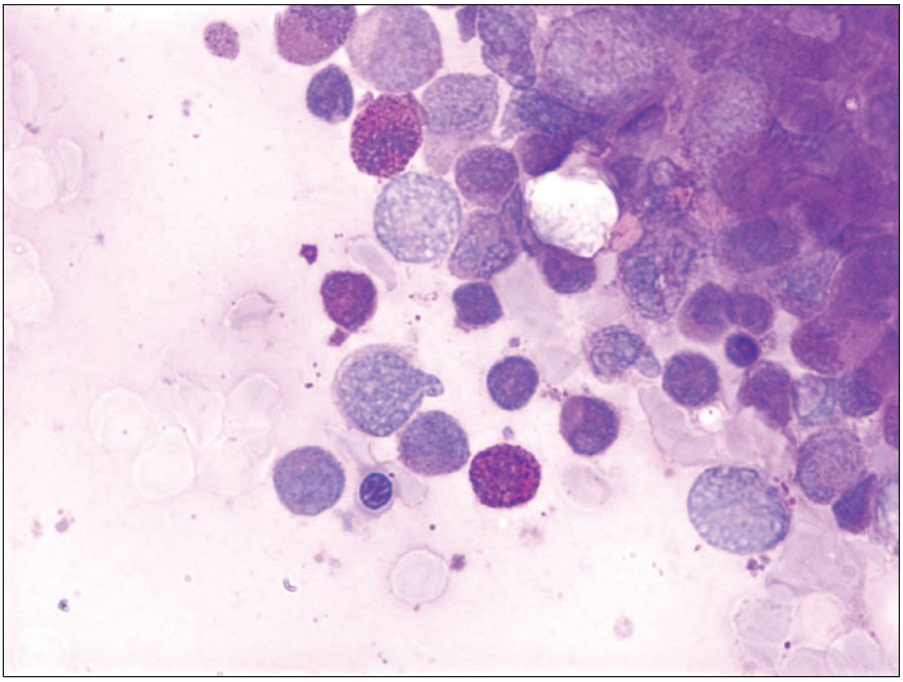


Figure IIB2-22

Periodic acid-Schiff stain.

Criteria

Peripheral Blood

- WBC is usually increased (range: 30×10^9/L–100×10^9/L)
  - Abnormal eosinophils are not usually found
  - Myeloblasts and monoblasts present

Bone Marrow

- >5% and <30% abnormal eosinophils
- Atypical eosinophils with monocytic or pseudo–Pelger-Huët features in the nuclei and abnormal basophilic granules

Cytochemistry

- Abnormal eosinophils are specific esterase and periodic acid-Schiff positive

M5a (Acute Monoblastic Leukemia)

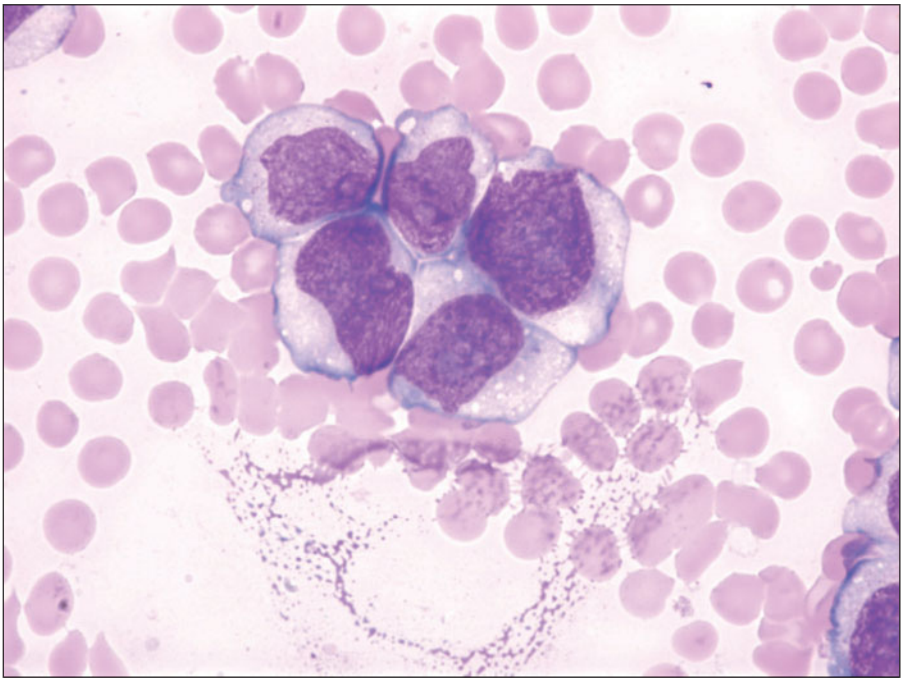


Figure IIB2-23

Peripheral blood smear.

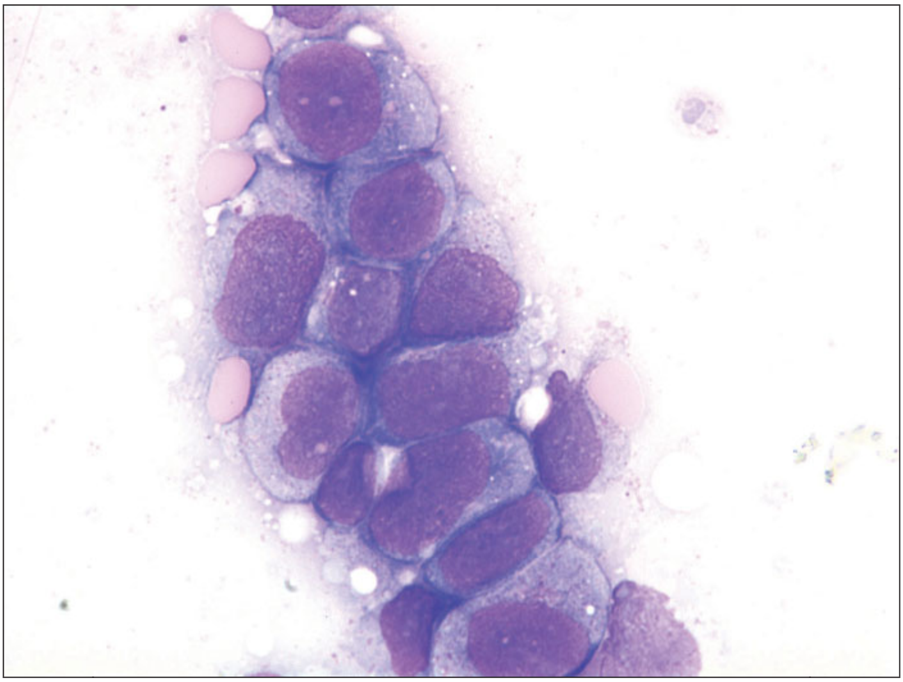


Figure IIB2-24

Bone marrow smear.

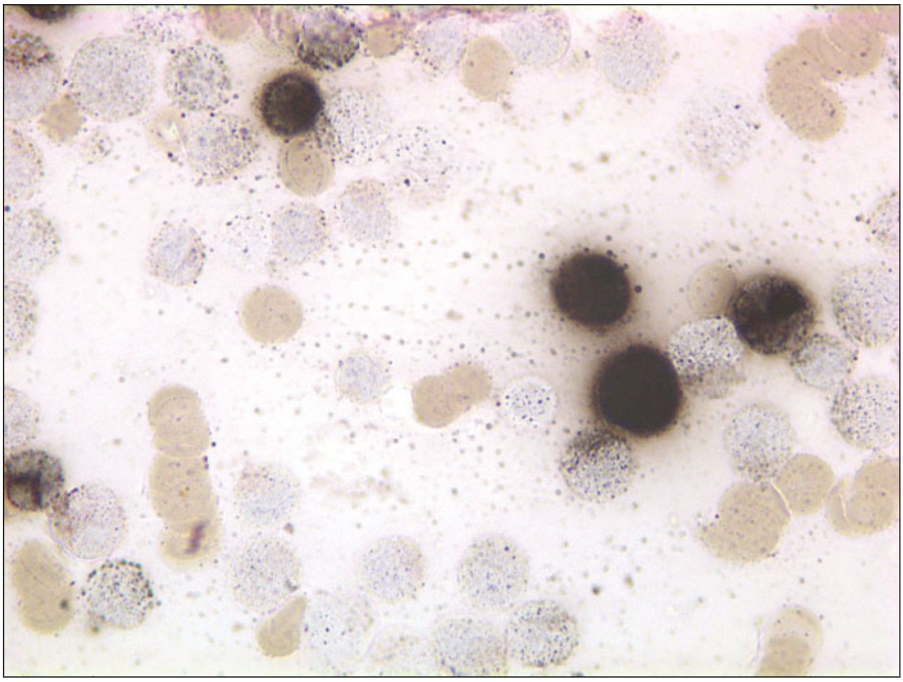


Figure **IIB2-25**

Nonspecific esterase stain.

Criteria

- Acute leukemia with almost total monocytic dominance

Peripheral Blood

- White blood cells are usually increased
- Blast morphology is variable
- Auer rods are usually absent

Bone Marrow

- <20% granulocytic precursors
- >80% are typically monoblasts
- Auer rods are usually present

Cytochemistry

- <20% are myeloperoxidase positive
- >80% are nonspecific esterase positive
- Naphthol AS-D chloroacetate—negative
- Naphthol AS-D acetate esterase ++++ (strong positivity) inhibited by sodium fluoride

M5b (Acute Monocytic Leukemia)

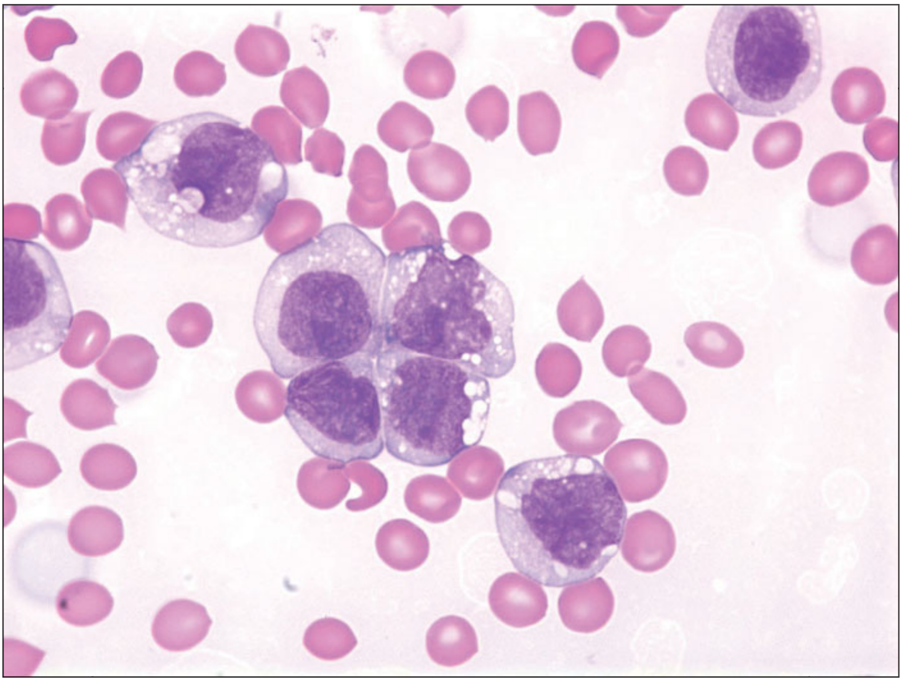


Figure IIB2-26

Peripheral blood smear.

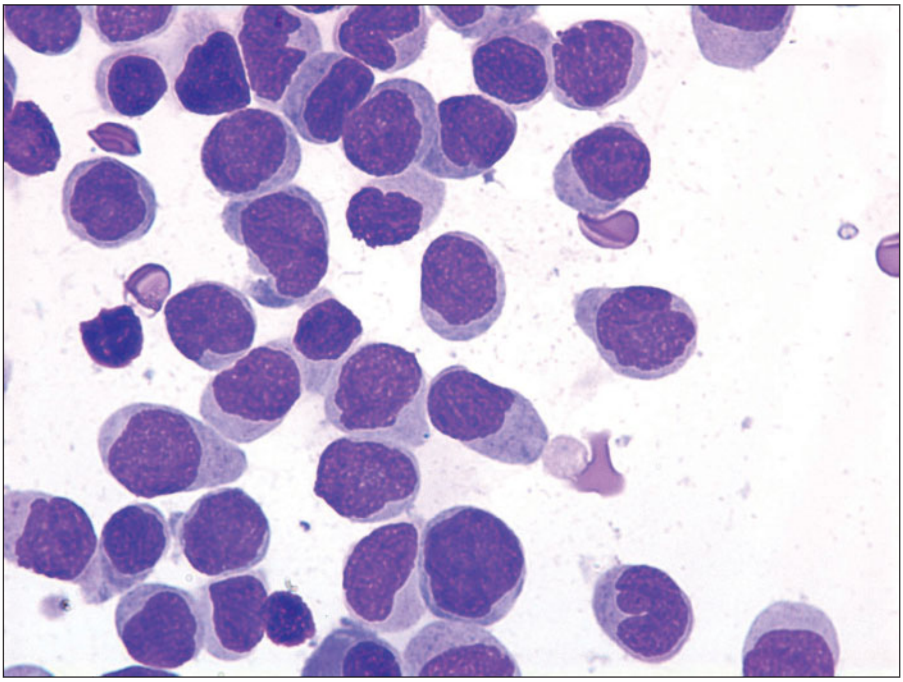


Figure IIB2-27

Bone marrow smear.

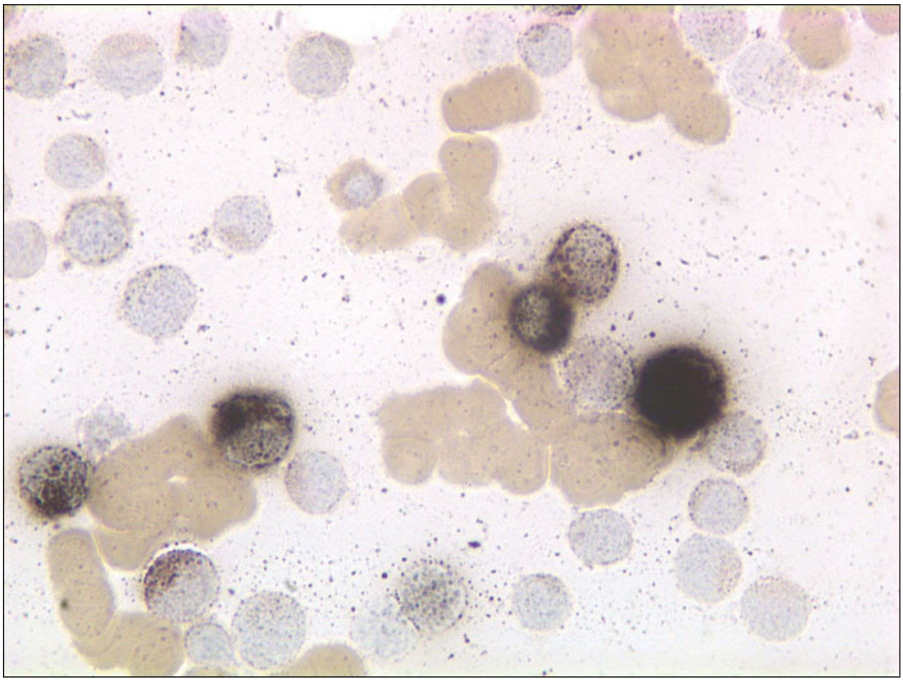


Figure **IIB2-28**

Nonspecific esterase stain.

Criteria

Peripheral Blood

- Monocytosis with the promonocyte as the predominant cell

Bone Marrow

- >80% immature monocytic component with the promonocyte as the predominant cell
- <20% are the granulocytic component

Cytochemistry

- <20% are myeloperoxidase positive cells
- Promonocytes may show some weak positivity with myeloperoxidase and are Sudan black B negative
- >80% of the cells are nonspecific esterase positive
- >80% of the cells are nonspecific esterase with sodium fluoride inhibition

M6a (Erythroleukemia)

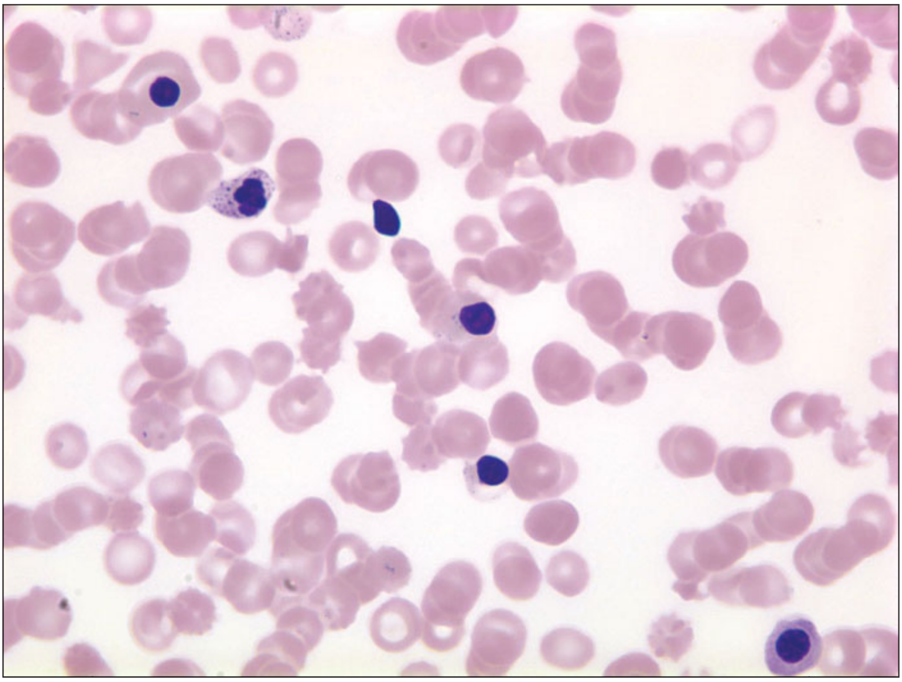


Figure IIB2-29

Peripheral blood smear.

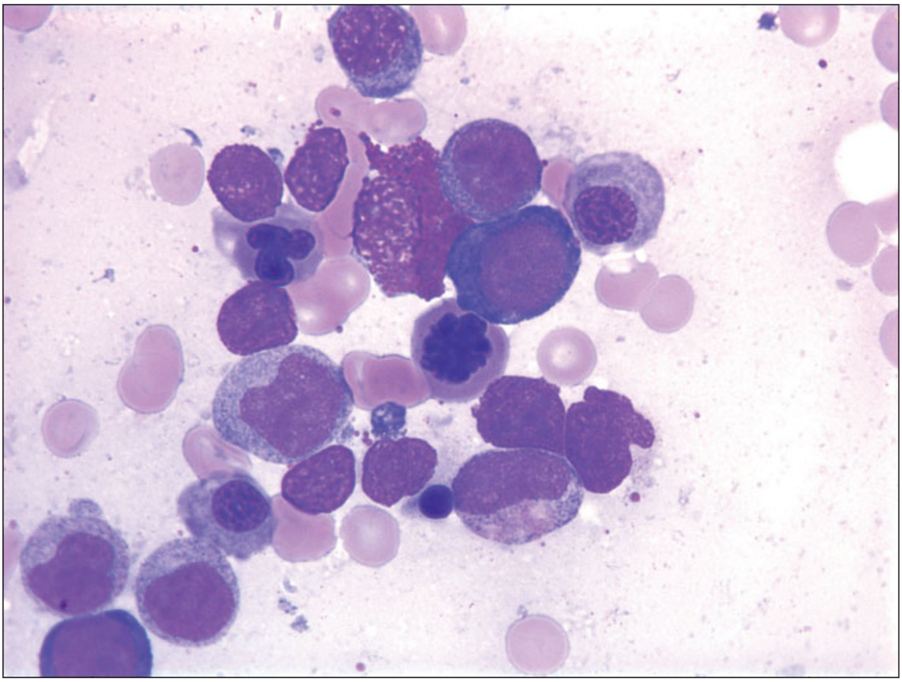


Figure IIB2-30

Bone marrow smear.

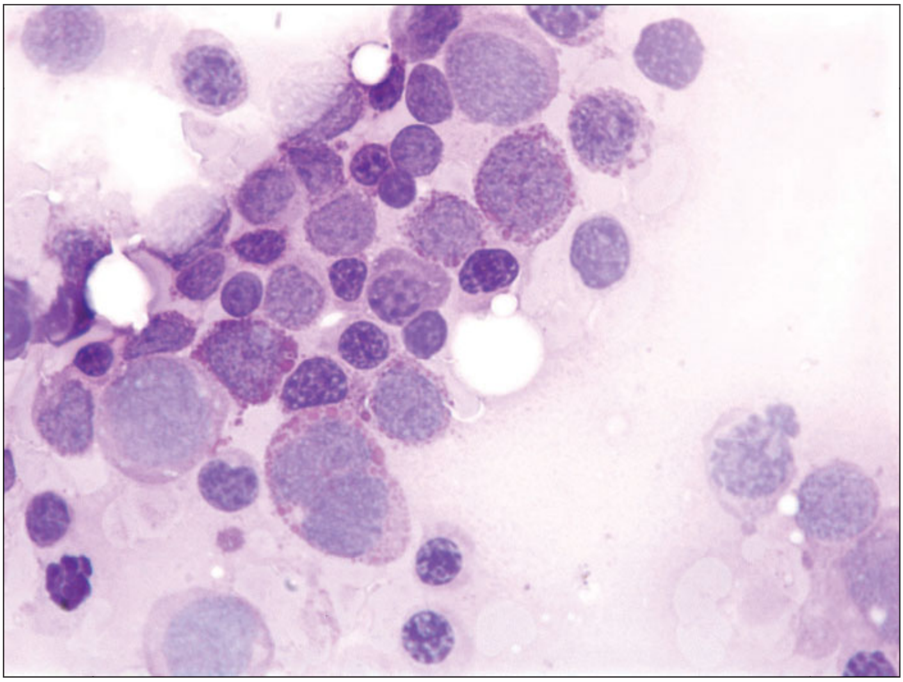


Figure **IIB2-31**

Periodic acid-Schiff stain.

Criteria

- Usually exhibits three phases and there is more myeloid involvement as the disease progresses

Peripheral Blood

- Normocytic/normochromic to macrocytic/normochromic anemia
- Anisocytosis, poikilocytosis, basophilic stippling, and nucleated red blood cells

Bone Marrow

- Acute and abnormal proliferation of erythroid and myeloid precursors
    - >50% erythroblasts (all nucleated cells)
    - >30% myeloblasts (non-erythroid cells) Type I and Type II
    - Trilineage dysplasia common—dyserythropoiesis, dysmegakaryopoiesis, dysgranulopoiesis

Cytochemistry

- Periodic acid-Schiff positive in early erythrocytic precursors
- Myeloperoxidase and Sudan black B show >3% positive in myeloblasts

M6b (Pure Erythroid Leukemia)

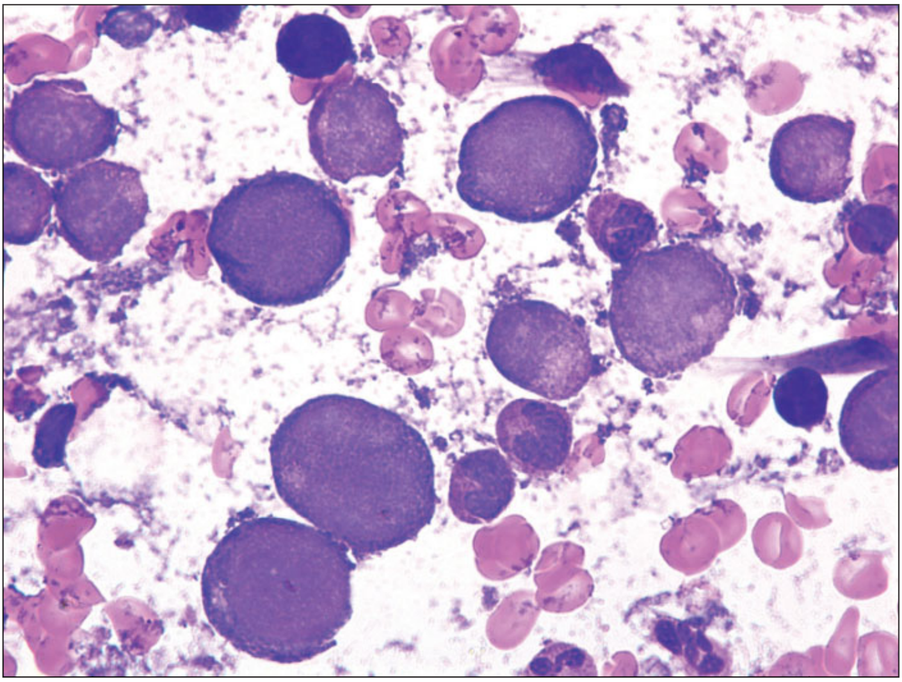


Figure **IIB2-32**

Bone marrow smear.

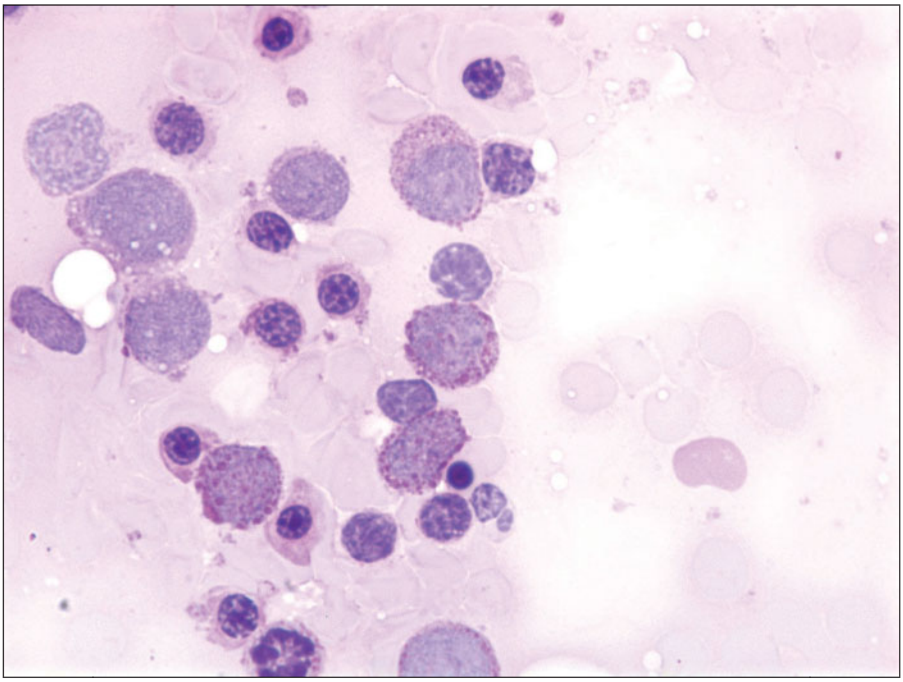


Figure **IIB2-33**

Periodic acid-Schiff stain.

Criteria

- Erythroid cell line malignancy with no myeloid involvement

Peripheral Blood

- Platelets are decreased
- Usually a macrocytic anemia

Bone Marrow

- >80% of the cells are erythroid precursors
- No evidence of myeloblastic component

Cytochemistry

- Myeloperoxidase, nonspecific esterase and Sudan black B negative
- Block positivity with periodic acid-Schiff

M7 (Acute Megakaryoblastic Leukemia)

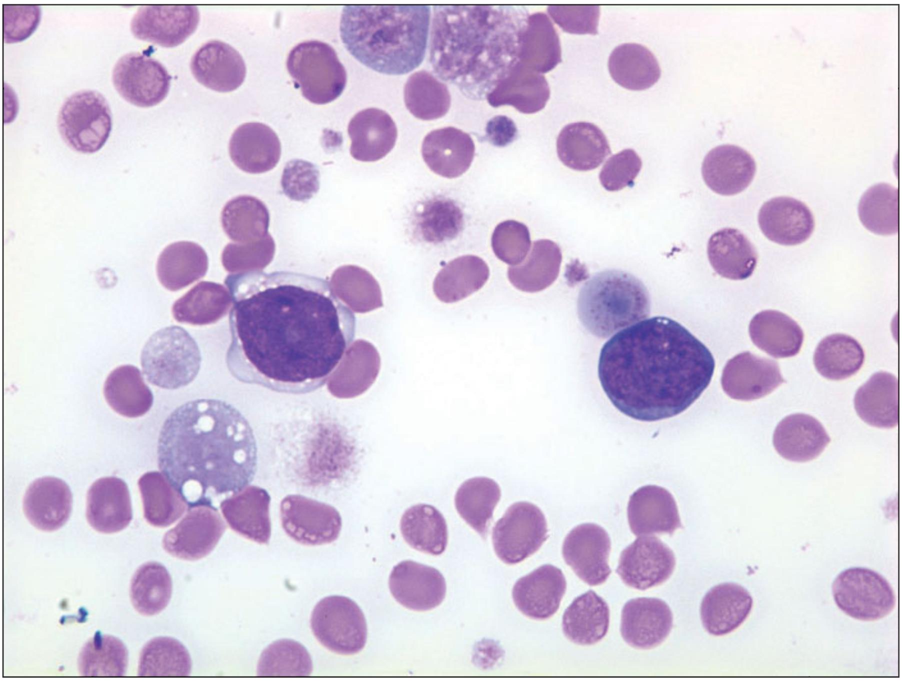


Figure IIB2-34

Peripheral blood smear.

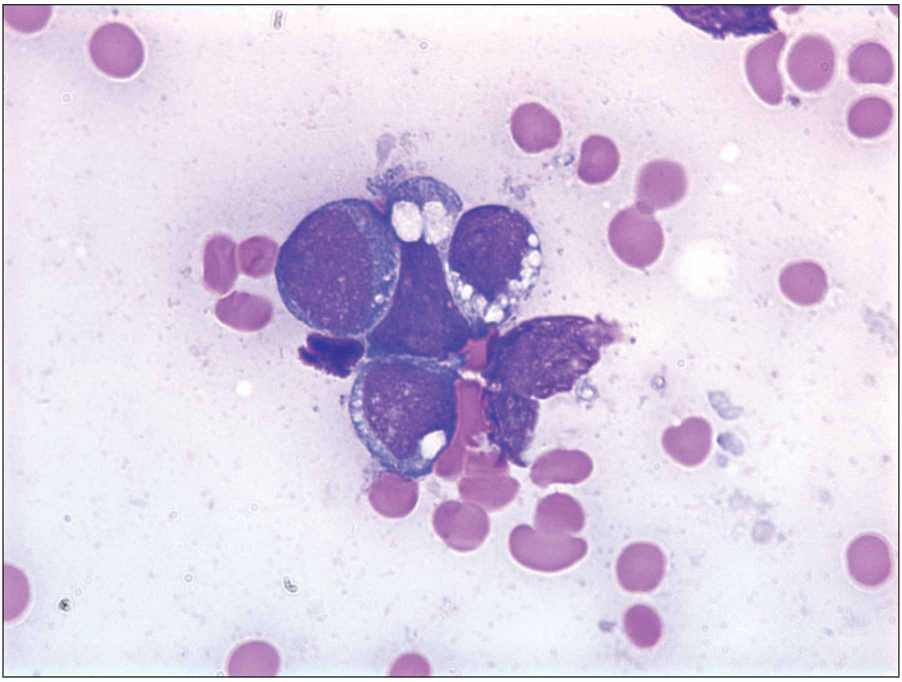


Figure IIB2-35

Bone marrow smear.

Criteria

Peripheral Blood

- Variable white blood cell count but usually decreased
- Normocytic/normochromic anemia
- Platelets are variable, bizarre, and atypical

Bone Marrow

- >30% blasts (usually hard to get an aspirate for quantitation of blasts)
- >50% megakaryocytic cells (megakaryoblasts, promegakaryocytes, and megakaryocytes)
- Megakaryoblasts are highly pleomorphic
- Small round cells with scant cytoplasm and dense heavy chromatin or larger vacuolated blasts

Cytochemistry

- Myeloperoxidase and Sudan black B negative
- Periodic acid-Schiff positive
- Nonspecific esterase (acetate) positive
- Nonspecific esterase (butyrate) negative

FAB CLASSIFICATION FOR L1–L3

L1 (Precursor Lymphoblastic Leukemia)

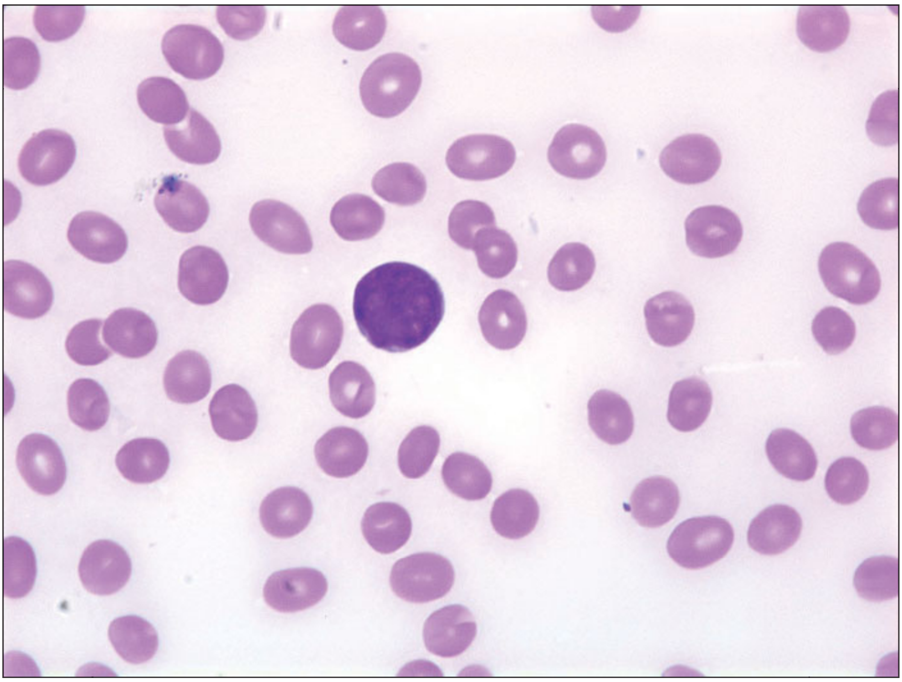


Figure IIB2-36

Peripheral blood smear.

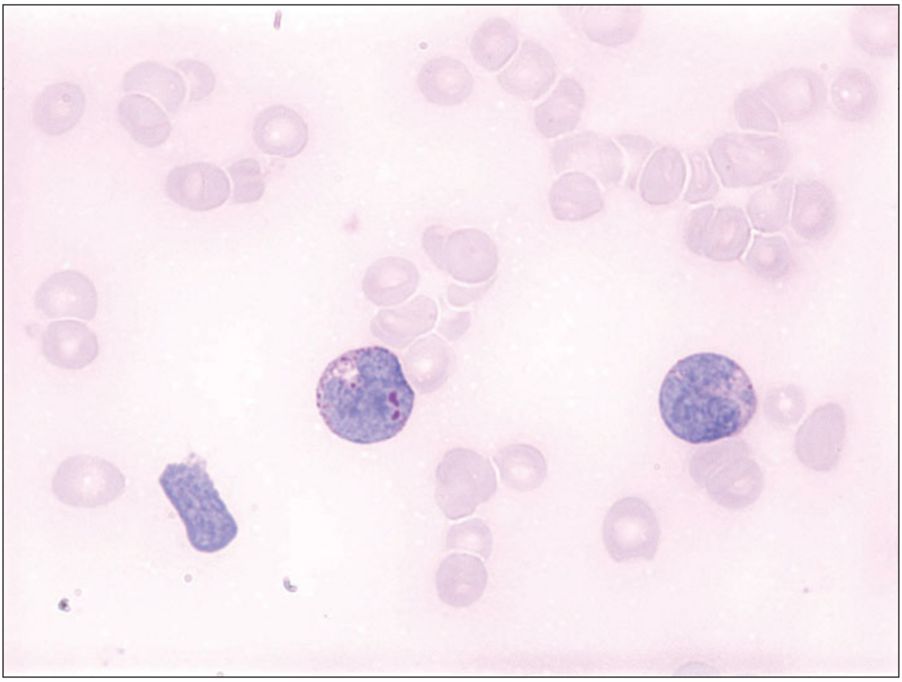


Figure IIB2-37

Periodic acid-Schiff stain.

Criteria

- Mutation of a single lymphoid stem cell causing proliferation of malignant lymphoblasts

Peripheral Smear

- Normocytic/normochromic anemia
- Decreased platelets
- White blood cells may be increased, decreased, or normal

Bone Marrow

- Hypercellular
- >25% blasts which are predominantly small blasts, up to twice the size of a normal small lymphocyte, nucleoli are not present and the cytoplasm is scant and only slightly or moderately basophilic

Cytochemistry

- Sudan black B, peroxidase, specific esterase and nonspecific esterase are negative
- Large block positivity with periodic acid-Schiff
- Focal positivity with acid phosphatase in T-cell blasts
- Terminal deoxynucleotidyl transferase (TdT) is positive in 90–95% in L1 and L2, negative in L3

L2 (Precursor Lymphoblastic Leukemia)

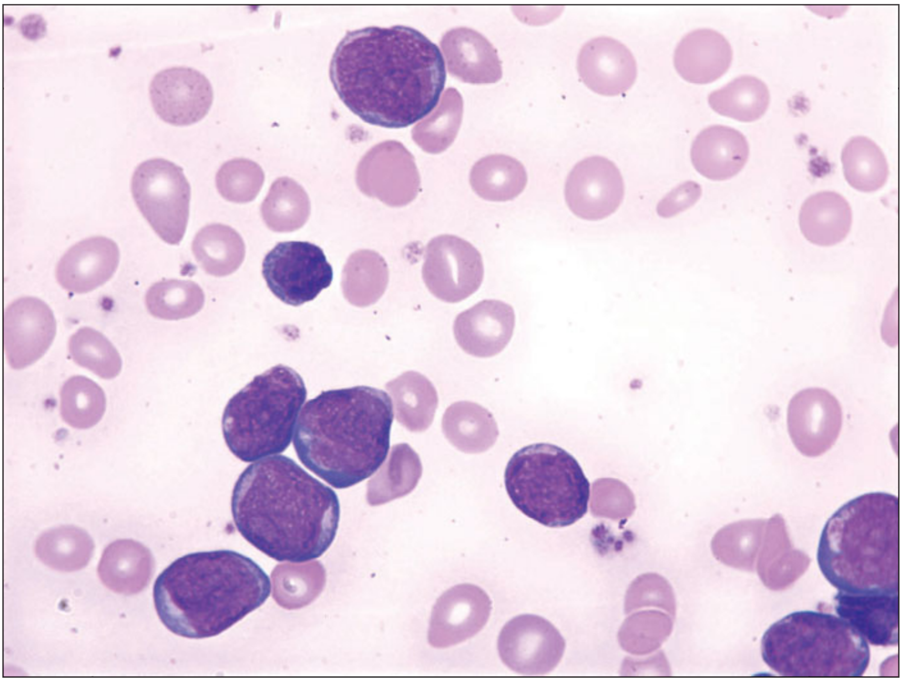


Figure IIB2-38

Peripheral blood smear.

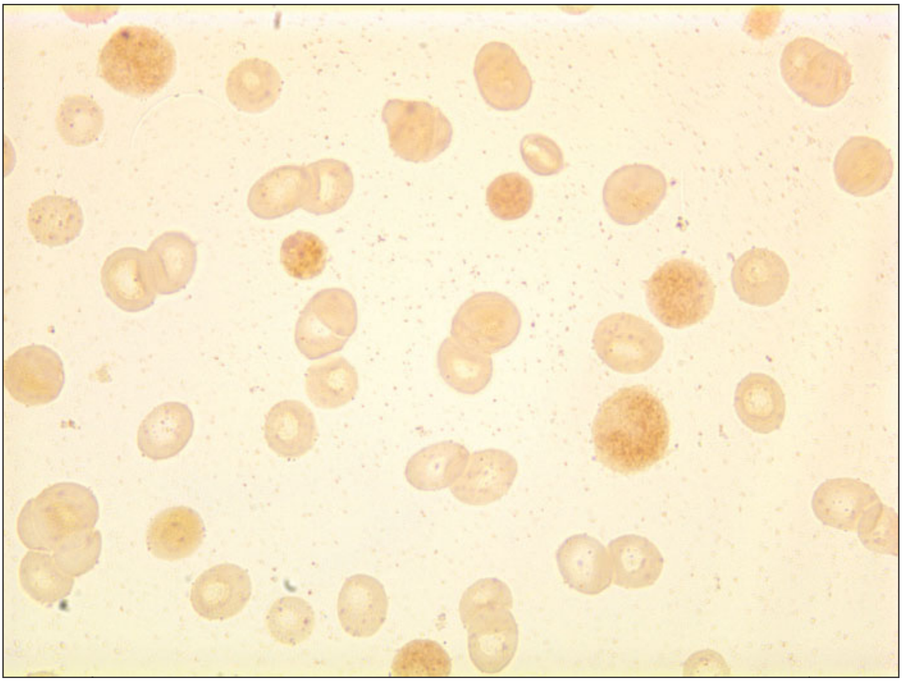


Figure IIB2-39

TdT stain.

Criteria

- Mutation of a single lymphoid stem cell causing proliferation of malignant lymphoblasts

Peripheral Blood

- Normocytic/normochromic anemia
- Platelets are often decreased
- White blood cells may be increased, normal, or decreased

Bone Marrow

- The blasts are larger than L1, heterogeneous in size, the nucleus is irregular with clefting and nucleoli are present

Cytochemistry

- Sudan black B, peroxidase, specific esterase and nonspecific esterase negative
- Large block positivity with periodic acid-Schiff
- Focal positivity with acid phosphatase in T-cell blasts
  - Terminal deoxynucleotidyl transferase (TdT) is positive in 90–95% in L1 and L2, negative in L3

L3 (Burkitt Type)

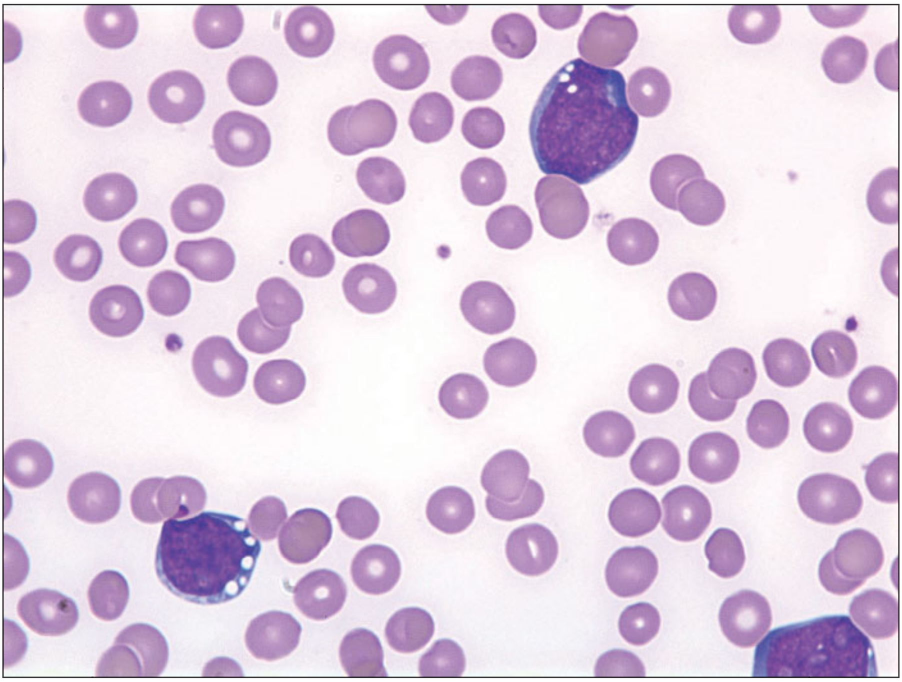


Figure **IIB2-40**

Peripheral blood smear.

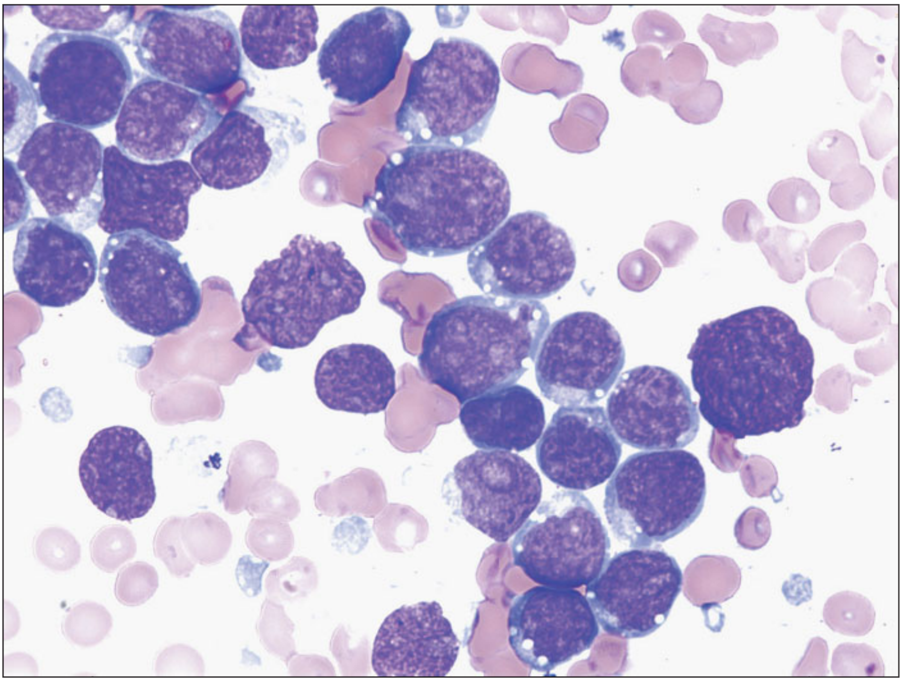


Figure **IIB2-41**

Bone marrow smear.

Criteria

- The lymphoblasts are similar in appearance to those found in Burkitt lymphoma
- Constitutes about 3–4% of precursor lymphoblastic leukemias in children and adults

Peripheral Blood

- Normocytic/normochromic anemia
- Decreased platelets are often seen
- White blood cells may be increased, decreased, or normal
- Blasts are larger than L1, have a round to oval nucleoli with fine, homogenous chromatin, and one or more nucleoli may be seen
- Cytoplasm of the blasts is deeply basophilic and vacuolated

Bone Marrow

- Hypercellular with blasts that are larger than L1, have a round- to oval-shaped nucleus with fine, homogenous chromatin and one or more nucleoli present
- Cytoplasm of the blasts is deeply basophilic and vacuolated

Cytochemistry

- Sudan black B, peroxidase, specific esterase and nonspecific esterase negative
- Periodic acid-Schiff negative
- Terminal deoxynucleotidyl transferase negative
- Oil red O positive

CHAPTER 3

World Health Organization (WHO) Classification of Hematologic Neoplasms

WHO CLASSIFICATION OF HEMATOLOGIC NEOPLASMS

Background

- First published in 2001 and revised in 2008 to stratify neoplasms according to lineage using clinical features, morphology including myeloid, lymphoid and histiocytic/dendritic cells, immunophenotypes, and genetic features
- The four major classifications of myeloid neoplasms based on these criteria are: Myeloproliferative neoplasms (MPN); Myelodysplastic syndromes/myeloproliferative neoplasms (MDS/MPN); Myelodysplastic syndromes (MDS); and Acute myeloid leukemia (AML)
- The following are used to classify the myeloid neoplasms
  - A manual 200 cell count of peripheral blood
  - A 500 nucleated cell count of the bone marrow
    - Greater than 20% blasts is used to define AML
      - Number of blasts in all nucleated marrow cells (except for acute erythroleukemia)
  - A trephine biopsy of the bone marrow provides information regarding overall cellularity
  - Cytochemistry staining of the bone marrow may be used to determine lineage of blasts
  - Immunophenotypes characterize antigen expression which is used to assist in lineage stratification and classification
  - Genetic abnormalities include gene rearrangements due to chromosomal translocations and gene mutations
- The WHO classification of the lymphoid neoplasm adopts the revised European-American lymphoid neoplasm (REAL) categories which use clinical features, morphology, immunophenotypes, and genetic features. They are: Precursor lymphoid neoplasms; Mature B-cell neoplasms; Mature T- and NK-cell neoplasms; and Hodgkin lymphoma

CHAPTER 4

Myeloproliferative Neoplasms

CHRONIC MYELOGENOUS LEUKEMIA, *BCR-ABL1* POSITIVE

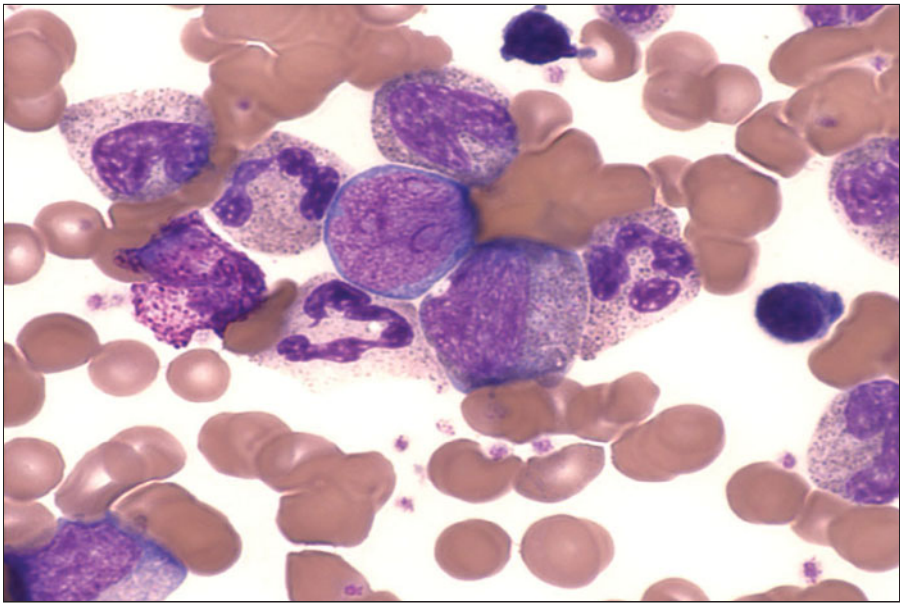


Figure IIB4-1

Peripheral blood smear.

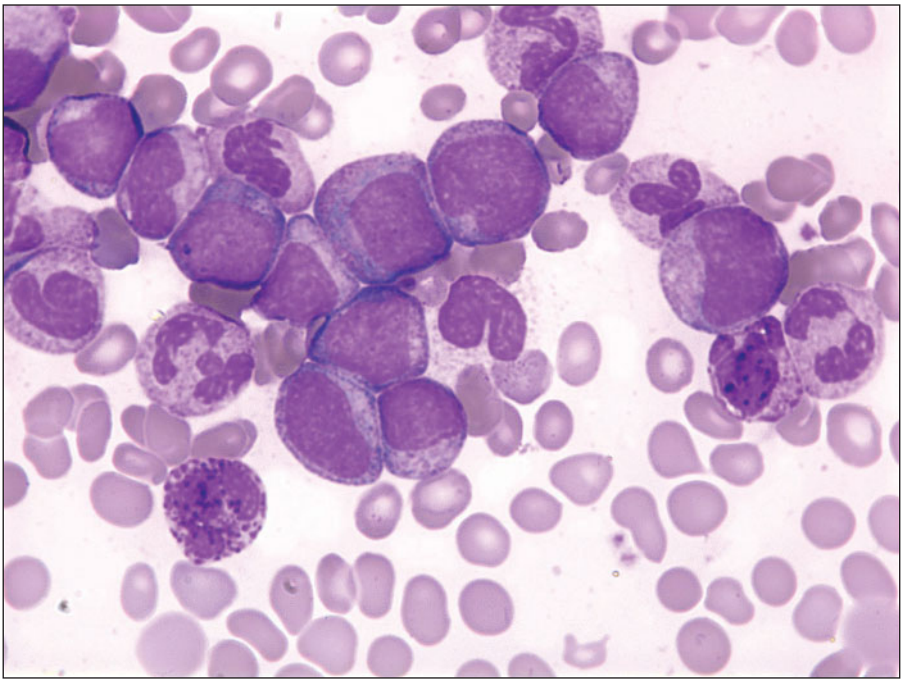


Figure IIB4-2

Bone marrow smear.

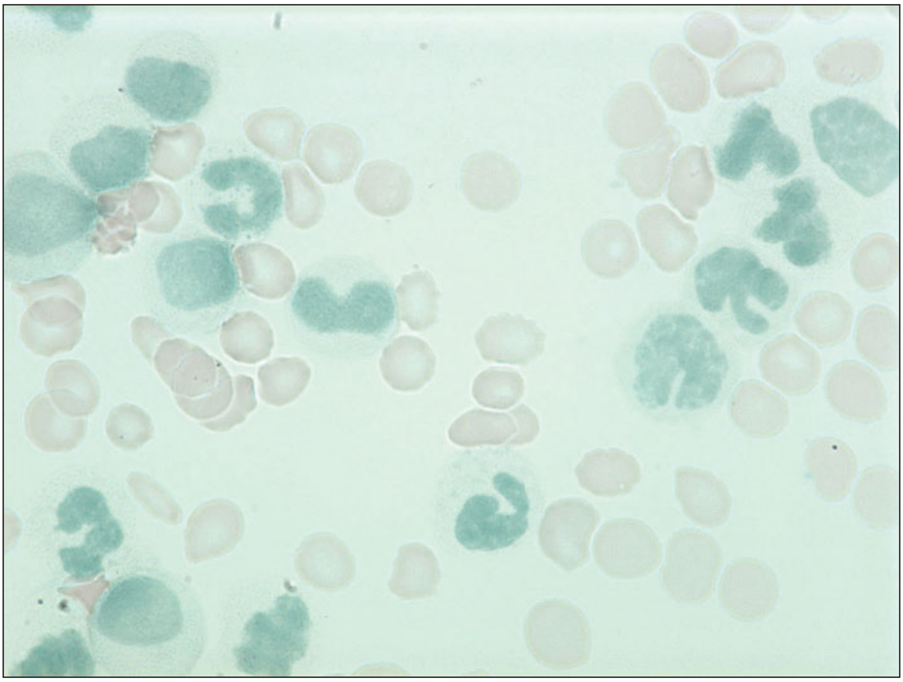


Figure IIB4-3

LAP stain.

Clinical Features

- Occurs most frequently in middle-aged people—peak age 50–60 years
- Accounts for about 25% of adult leukemias
- Weight loss, night sweats, anorexia, visual disturbances, and bone pain
- Splenomegaly and hepatomegaly
- Anemia, bleeding disorders, and gout

Pathology

- Three stages
  - Chronic stable phase
  - Accelerated phase
  - Blastic phase
- Normal bone marrow cells are replaced with cells containing an abnormal G-group chromosome called the Philadelphia or Ph chromosome (90–95% of cases)
- Double Philadelphia chromosome is associated with blastic transformation and accelerated phase

Laboratory Features

White Blood Cells

- Increased to ≥170 × 10^9/L
- Entire maturation series of granulocytes is seen but no toxic changes
- Eosinophilia
- Basophilia

Red Blood Cells

- Normocytic/normochromic anemia
- Occasional nucleated red blood cells

Platelets

- Typically increased but may be normal or decreased

Bone Marrow

- 90–100% cellularity
- M:E ratio 10:1 to 50:1
- Megakaryocytes are reduced in number and size
- Pseudo-Gaucher cells and sea-blue histiocytes can be observed if there is increased cell turnover

Cytochemistry

- Leukocyte alkaline phosphatase level markedly decreased (score is usually ≤10)
- Neutrophils in the chronic phase have markedly decreased neutrophil alkaline phosphatase
- In the blastic phase, the blasts may have strong, weak or no myeloperoxidase activity but express antigen associated with granulocytic, monocytic, lymphocytic, megakaryocytic and/or erythroid differentiation

Genetics

- Translocation of material from the long arm of 22 to the long arm of 9 and from 9 to 22
- Fuses the *BCR* gene from chromosome 22 with regions of the *ABL* gene on chromosome 9

Diagnostic Criteria—Chronic Phase

Peripheral Blood

- Leukocytosis due to neutrophils in various stages of maturation
- Usually <2% blasts
- Basophilia
- <3% monocytes
- Normal or increased platelet count
- Mild anemia

Bone Marrow

- Hypercellular
- <5% blasts
- Smaller than normal megakaryocytes with hypolobulated nuclei
- Reticulin fibers increased
- Eosinophils may be increased
- Pseudo-Gaucher cells and sea-blue histiocytes may be seen

Diagnostic Criteria—Accelerated Phase

Peripheral Blood

- One or more of the following:
  - 10–19% myeloblasts
  - ≤20% basophils
  - Persistent platelet count >1000 × 10^9/L or <100 × 10^9/L
  - Increasing numbers of white blood cells

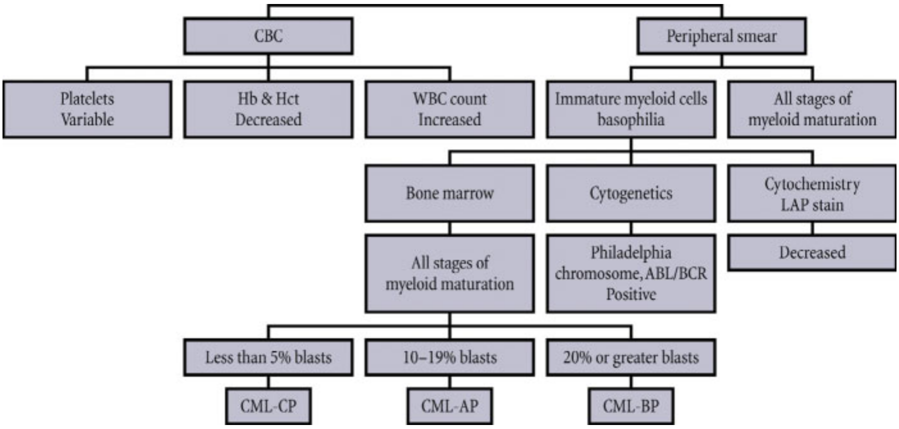
Bone Marrow

- One or more of the following:
  - 10–19% myeloblasts
  - Dysgranulopoiesis
  - Dysmegakaryopoiesis
  - Marked collagen or reticulin fibrosis

Diagnostic Criteria—Blastic Phase

- ≥20% blasts in blood or bone marrow
- Extramedullary proliferation of blasts
- Presence of large clusters of blasts in bone marrow

Diagnostic Scheme


CBC
Peripheral smear
Platelets Variable
Hb & Hct Decreased
WBC count Increased
Immature myeloid cells basophilia
All stages of myeloid maturation
Bone marrow
Cytogenetics
Cytochemistry LAP stain
All stages of myeloid maturation
Philadelphia chromosome, ABL/BCR Positive
Decreased
Less than 5% blasts
10–19% blasts
20% or greater blasts
CML-CP
CML-AP
CML-BP

CHRONIC NEUTROPHILIC LEUKEMIA

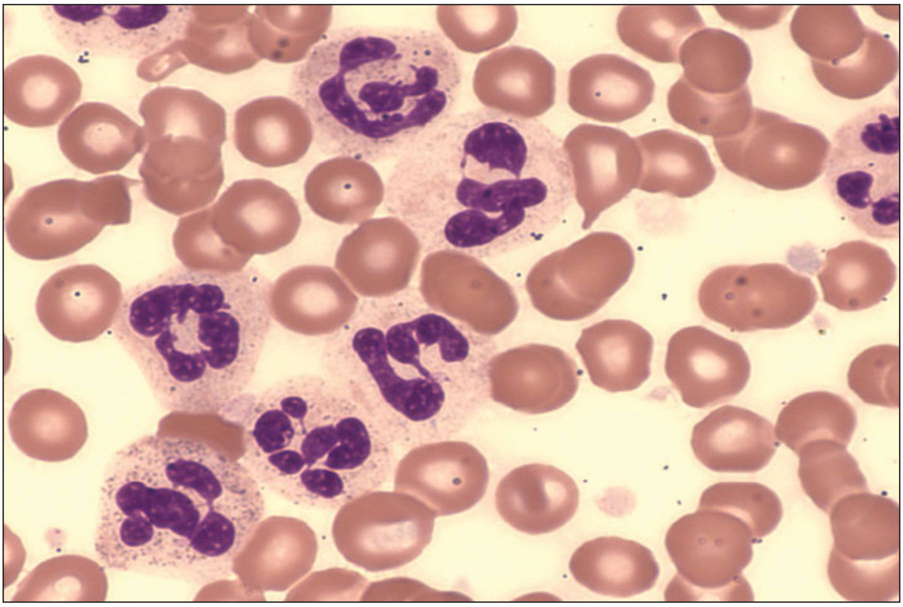


Figure IIB4-4

Peripheral blood smear.

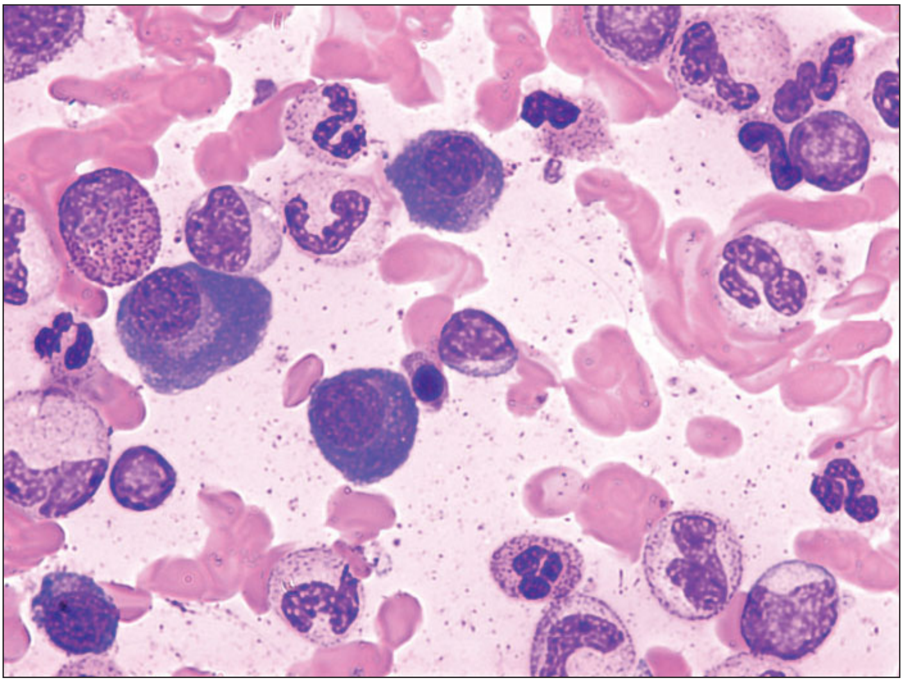


Figure IIB4-5

Bone marrow smear.

Clinical Features

- Usually 50 years or older
- Equal gender distribution
- Splenomegaly
- Hepatomegaly

Pathology

- Very rare
- Seen with plasma dyscrasias
- Clonal disorder

Laboratory Features

White Blood Cells

- Persistent neutrophilia with >25 × 10^9/L count
- Predominant cell is the neutrophil (>80%) with a possible increase in bands
- <1% myeloblasts
- Monocytes <1 × 10^9/L

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Normal

Bone Marrow

- Granulocytic hypercellularity
- M:E ratio about 5:1 to 25:1
- <5% myeloblasts
- No myelofibrosis
- About 20% of cases are associated with multiple myeloma

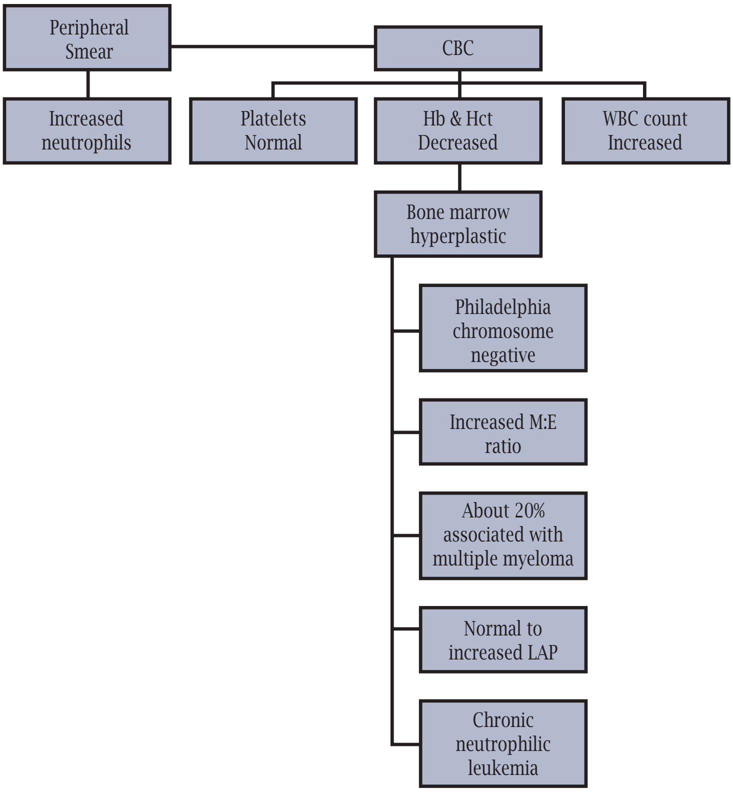
Cytochemistry

- Neutrophilic alkaline phosphatase is normal or increased

Genetics

- 90% of the cases have no abnormality
- Philadelphia chromosome or *BCR-ABL1* fusion genes are absent

Diagnostic Scheme


Peripheral Smear
CBC
Increased neutrophils
Platelets Normal
Hb & Hct Decreased
WBC count Increased
Bone marrow hyperplastic
Philadelphia chromosome negative
Increased M:E ratio
About 20% associated with multiple myeloma
Normal to increased LAP
Chronic neutrophilic leukemia

POLYCYTHEMIA VERA

- See Section A, Chapter 1 for description

PRIMARY MYELOFIBROSIS (PMF)

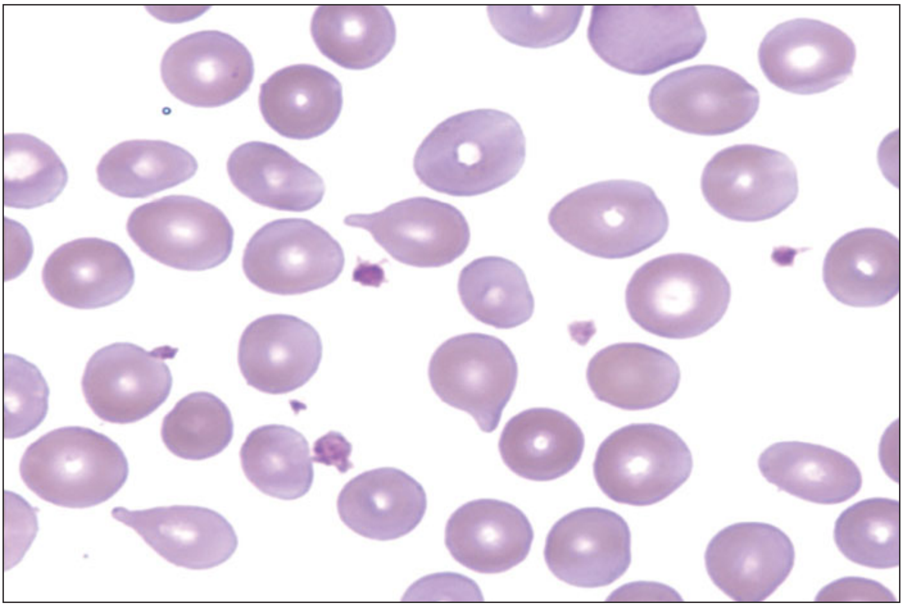


Figure IIB4-6

Peripheral blood smear.

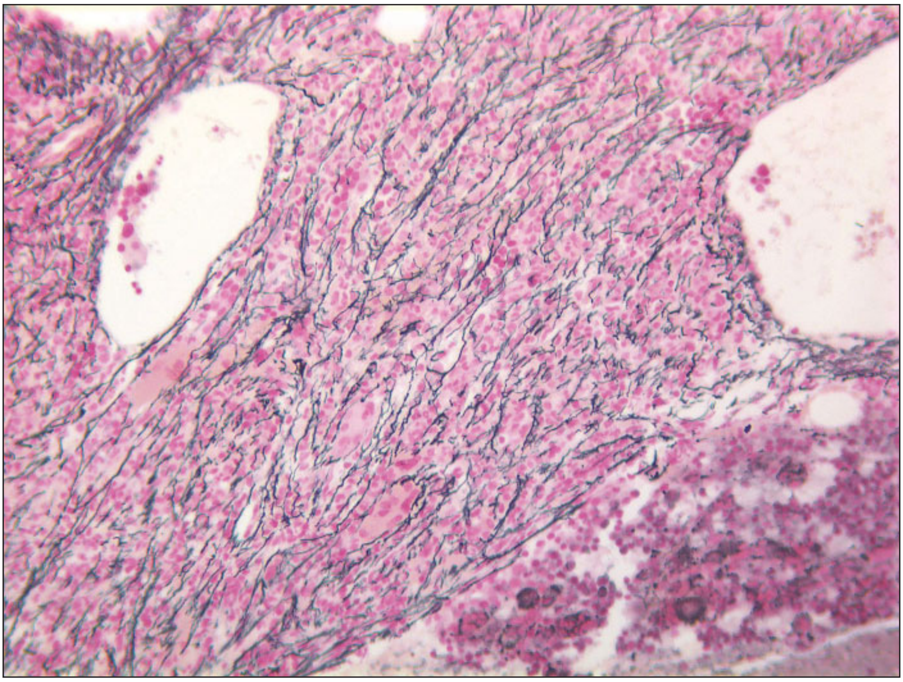


Figure IIB4-7

Bone marrow biopsy.

Clinical Features

- Also known as agnogenic myeloid metaplasia (AMM) or chronic idiopathic myelofibrosis (CIMF) or myelofibrosis/sclerosis with myeloid metaplasia (MMM) or idiopathic myelofibrosis
- Occurs in elderly persons
- Fatigue, weakness, weight loss, gouty arthritis, petechiae, and purpura
- Lymphadenopathy
- No or mild hepatosplenomegaly in the prefibrotic stage and moderate to marked hepatosplenomegaly in the fibrotic state
- Anemia and pallor

Pathology

- Clonal stem cell disorder that involves the multipotential stem cell
- Fibrosis is a secondary abnormality
- Growth factors stimulate fibroblastic proliferation

Laboratory Features

White Blood Cells

- Count is usually $<30.0 \times 10^9/L$
- Immature cells in the myeloid series

Red Blood Cells

- Nucleated red blood cells
- Normocytic/normochromic anemia
- Dacryocytes (tear-shaped red blood cells) are present

Platelets

- Normal, decreased, or increased
- Morphology may be abnormal

Bone Marrow

- Hypocellular with marked increase in reticulin and/or collagen fibrosis

Prefibrotic Stage

- Mild anemia
- No or mild leukoerythroblastosis
- No or minimal poikilocytosis
- Mild to moderate leukocytosis
- Mild to marked thrombocytosis
- Hypercellular marrow
- Neutrophilic and megakaryocytic proliferation

Fibrotic Stage

- Leukoerythroblastosis
- Poikilocytosis
- Moderate to marked anemia
- Variable white blood cell count
- Variable platelet count
- Decreased marrow cellularity
- Increased marrow reticulin and collagen
- Megakaryocytic proliferation

Cytochemistry

- Reticulin stain is increased

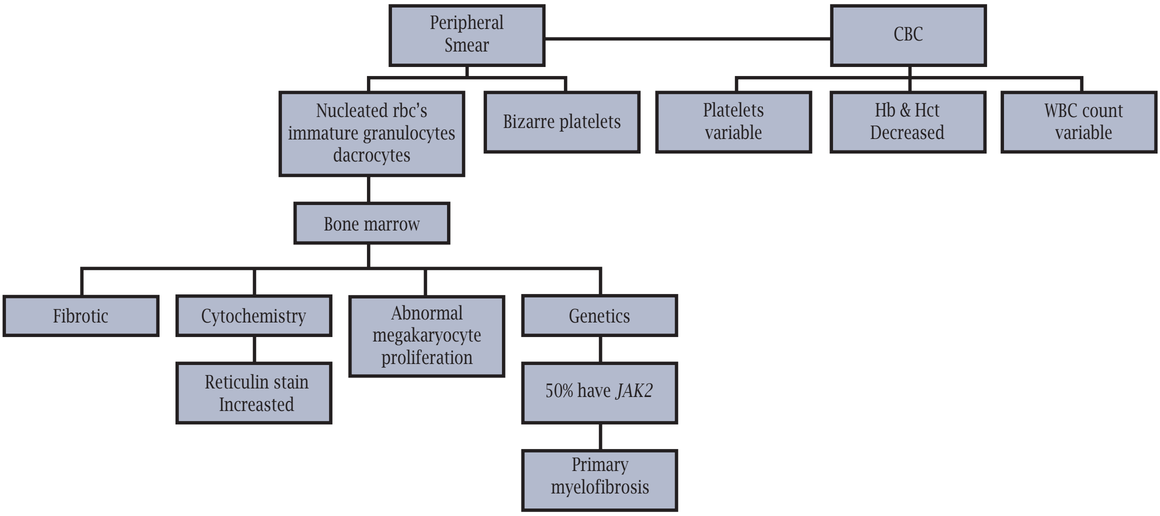
Immunophenotype

- No abnormal phenotypic features

Genetics

- 50% of patients have the *JAK2 V617F* mutation
- No specific genetic defect has been identified
- 30% have cytogenetic abnormalities but no Philadelphia chromosome or *BCR-ABL1* fusion gene

Diagnostic Scheme


Peripheral Smear
CBC
Nucleated rbc's immature granulocytes dacrocytes
Bizarre platelets
Platelets variable
Hb & Hct Decreased
WBC count variable
Bone marrow
Fibrotic
Cytochemistry
Abnormal megakaryocyte proliferation
Genetics
Reticulin stain Increasted
50% have *JAK2*
Primary myelofibrosis

ESSENTIAL THROMBOCYTHEMIA (ET)

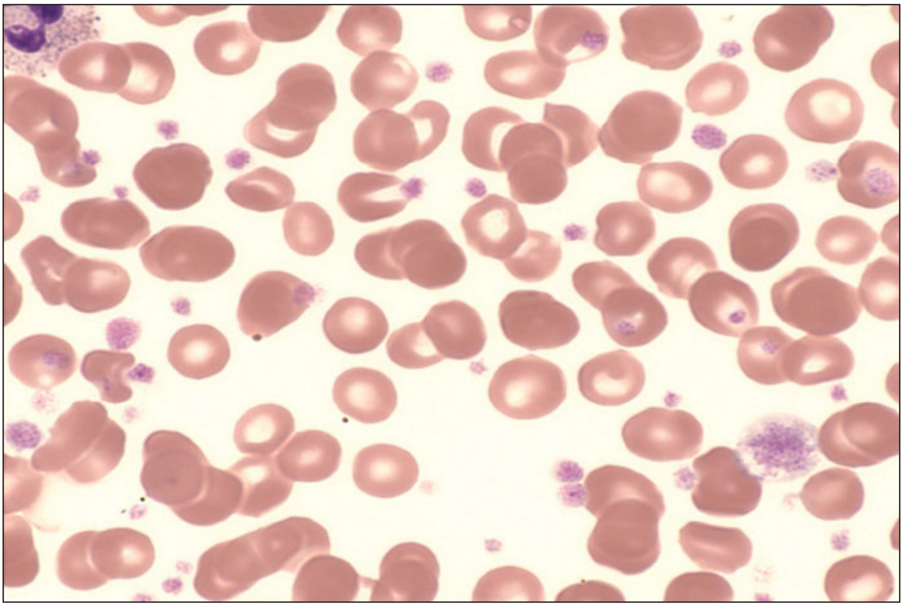


Figure **IIB4-8**

Peripheral blood smear.

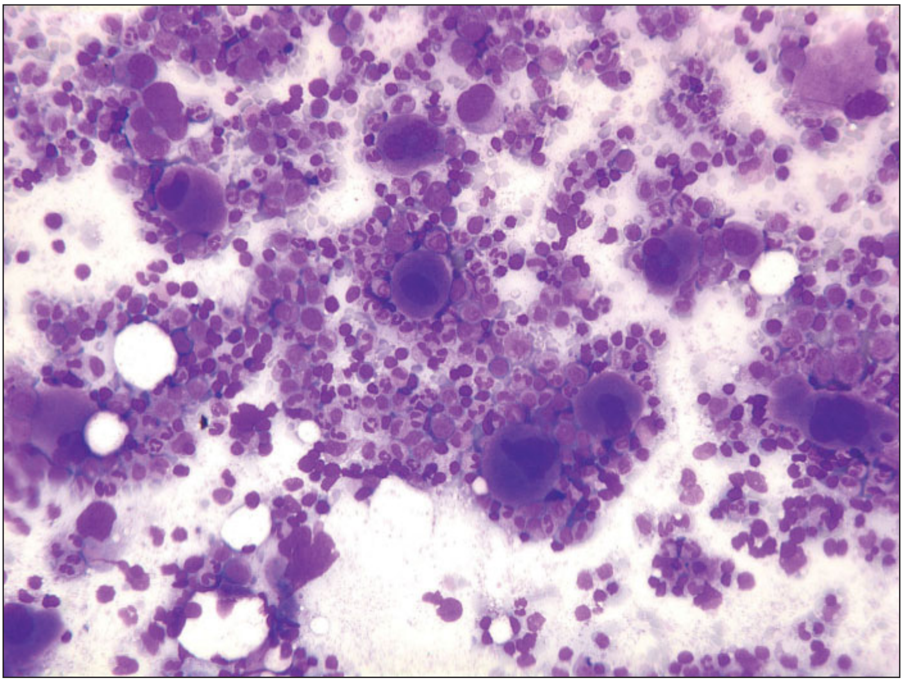


Figure **IIB4-9**

Bone marrow smear.

Clinical Features

- Also known as primary thrombocytosis or idiopathic thrombocytosis
- Splenomegaly
- Epistaxis, hemorrhage, or thrombosis

Pathology

- Patients are usually older than 50 years
- Clonal abnormality involving the megakaryocytic lineage
- Absence of Philadelphia chromosome
- Other causes for thrombocytosis must be excluded

Laboratory Features

White Blood Cells

- Usually normal or mildly increased
- Basophilia absent or minimal

Red Blood Cells

- Normocytic/normochromic anemia
- Microcytic, hypochromic anemia if there is gastrointestinal tract blood loss
- Red blood cell mass not elevated
- No dacryocytes or leukoerythroblastosis

Platelets

- Thrombocytosis with counts >450 × 10^9/L but typically higher
- Platelets vary in size
- Bizarre shapes with agranular forms are not uncommon

Bone Marrow

- Normocellular or moderately hypercellular
- Increased numbers of large, to giant megakaryocytes
- Megakaryocytes mass increased
- Increased megakaryocytes arranged in clusters or evenly dispersed

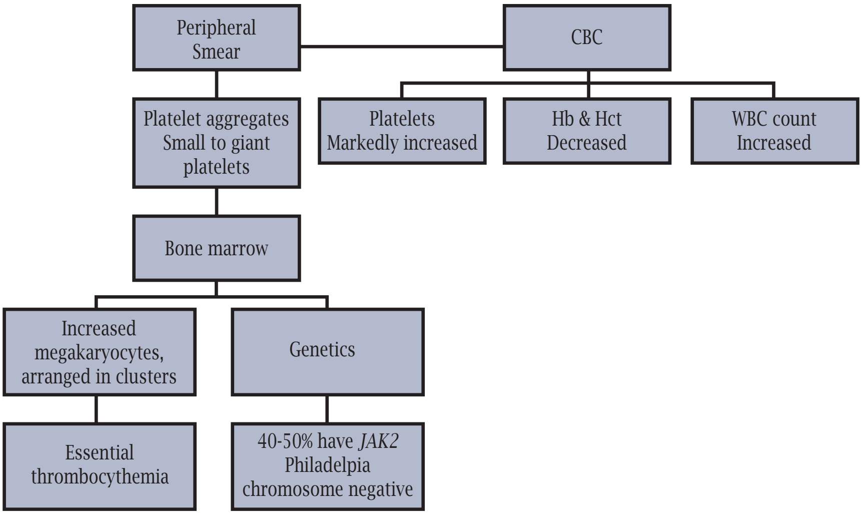
Immunophenotype

- No abnormal phenotypes

Genetics

- No specific genetic or cytogenetic abnormalities
- 40–50% of cases carry the *JAK2 V617F* mutation

Diagnostic Scheme


Peripheral Smear
CBC
Platelet aggregates Small to giant platelets
Platelets Markedly increased
Hb & Hct Decreased
WBC count Increased
Bone marrow
Increased megakaryocytes, arranged in clusters
Genetics
Essential thrombocythemia
40-50% have *JAK2* Philadelpia chromosome negative

CHRONIC EOSINOPHILIC LEUKEMIA, NOT OTHERWISE SPECIFIED (CEL, NOS)

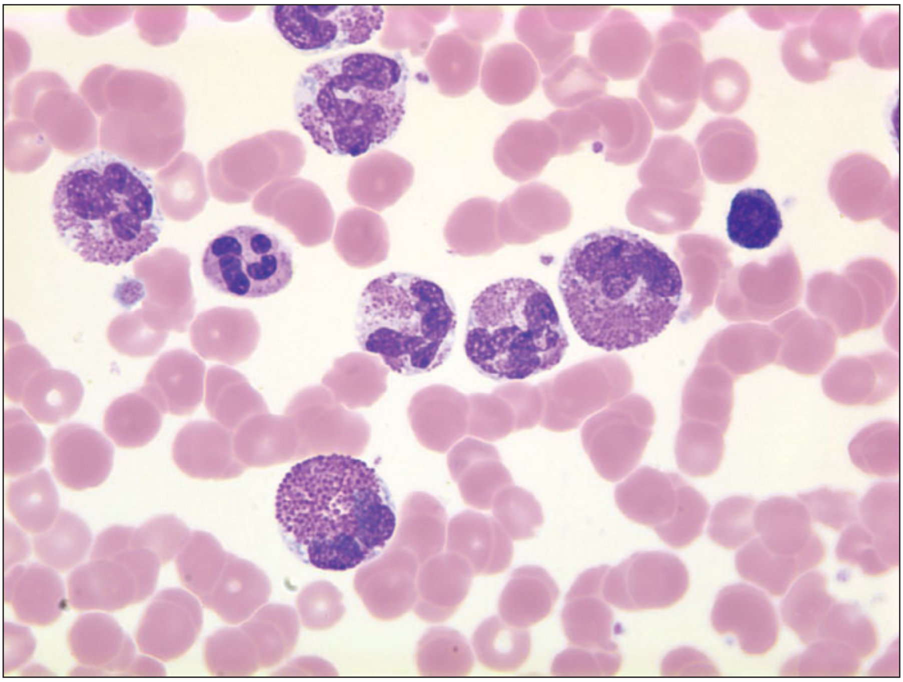


Figure IIB4-10

Peripheral blood smear.

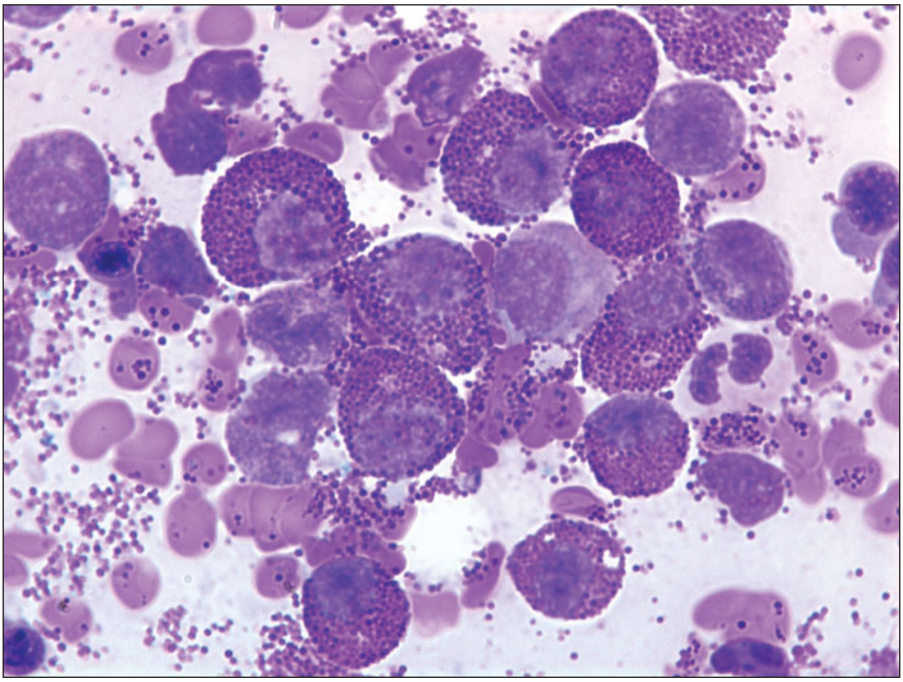


Figure IIB4-11

Bone marrow smear.

Clinical Features

- Many patients are asymptomatic
- Hepatosplenomegaly
- Skin involvement
- Fever and weight loss
- Central nervous system irregularities, congestive heart failure, and pulmonary fibrosis

Pathology

- Rare
- Usually middle-aged males are affected
- Clonal abnormality

Laboratory Features

White Blood Cells

- Persistent absolute eosinophilia ($>1.4 \times 10^9$/L)
- 30–70% eosinophils
- Count is usually $>30.0 \times 10^9$/L
- <20% blasts
- Eosinophils exhibit sparse granulation with clear areas of cytoplasm, vacuoles, and may be increased in size

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- Eosinophilia with increasing myeloid immaturity
- <20% blasts
- Charcot–Leyden crystals are often present
- Increased number of eosinophilic myelocytes

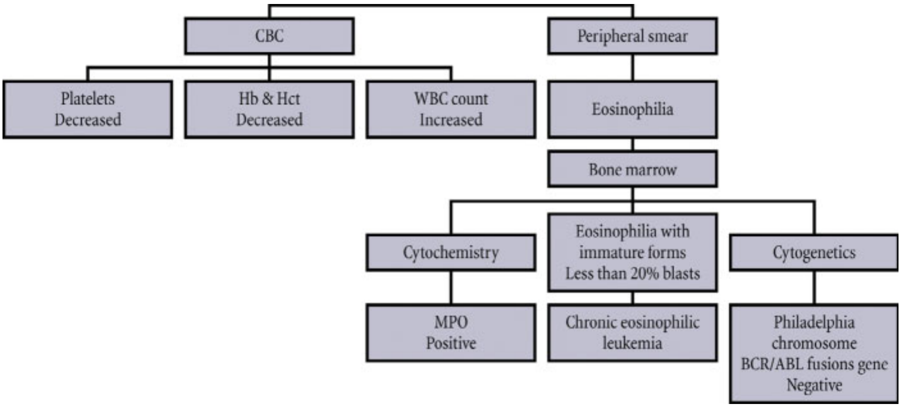
Immunophenotype

- No specific abnormalities

Genetics

- No single or specific cytogenetic or molecular genetic abnormalities
- Some cases have rearrangement of *PDGFRA, PDGFRB,* or *FGFR1* are specifically excluded

Diagnostic Scheme


CBC
Peripheral smear
Platelets Decreased
Hb & Hct Decreased
WBC count Increased
Eosinophilia
Bone marrow
Cytochemistry
Eosinophilia with immature forms Less than 20% blasts
Cytogenetics
MPO Positive
Chronic eosinophilic leukemia
Philadelphia chromosome BCR/ABL fusions gene Negative

MASTOCYTOSIS

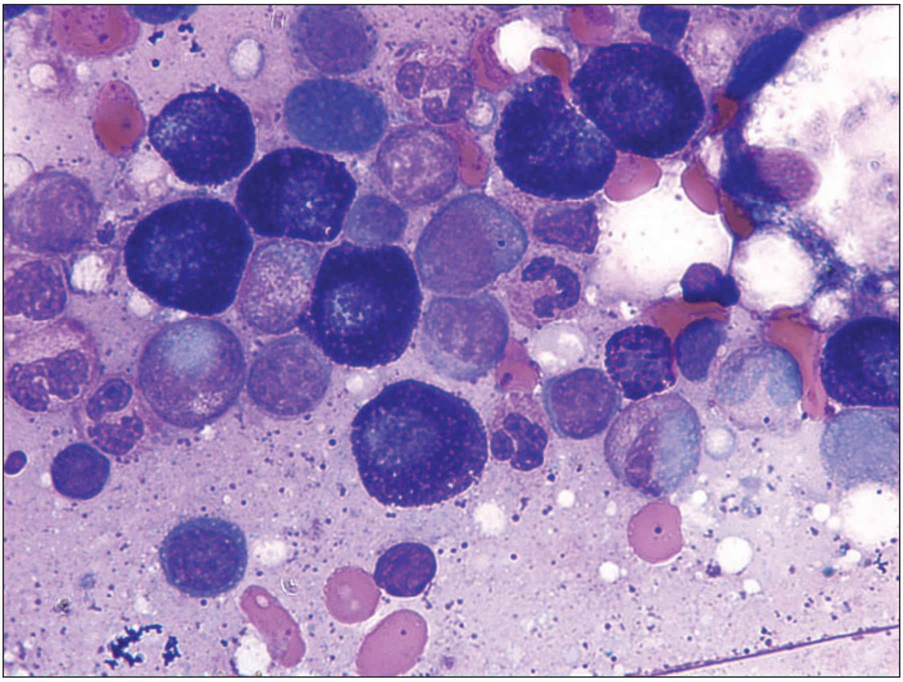


Figure IIB4-12

Bone marrow smear.

Clinical Features

- The disorder is heterogeneous and may range from skin lesions to multi-organ failure
- In cutaneous mastocytosis (CM), the mast cell infiltration remains confined to the skin
- In systemic mastocytosis (SM), at least one extracutaneous organ is involved
- Mast cell leukemia (MCL) is a highly aggressive form of SM
- Common symptoms are fever and weight loss

Pathology

- A clonal, neoplastic proliferation of mast cells that accumulate in one or more organ systems
- Presence of clusters of abnormal mast cells

Laboratory Features

White Blood Cells

- May have 10% or more mast cells
- Mast cells are morphologically abnormal

Red Blood Cells

- Mild to moderate normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- ≥20% mast cells
- Diffuse, compact infiltrate with reduction in fat cells and normal hematopoietic cells
- Mast cells are atypical with hypogranular cytoplasm, irregularly shaped monocytoid or bilobulated nuclei

Cytochemistry

- Toluidine blue may be positive

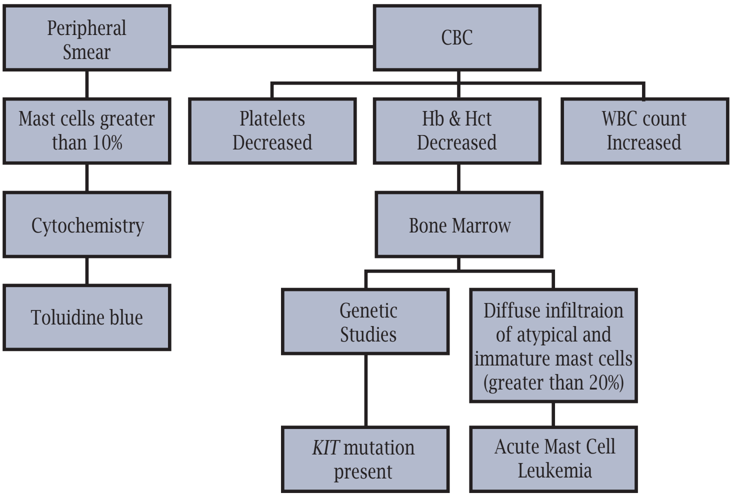
Immunophenotype

- Express CD9, CD33, CD45, CD68, and CD117
- Lack CD14, CD15, and CD16
- React with antibodies against tryptase

Genetics

- Frequently associated with point mutations within *KIT*

Diagnostic Scheme


Peripheral Smear
CBC
Mast cells greater than 10%
Platelets Decreased
Hb & Hct Decreased
WBC count Increased
Cytochemistry
Bone Marrow
Toluidine blue
Genetic Studies
Diffuse infiltraion of atypical and immature mast cells (greater than 20%)
KIT mutation present
Acute Mast Cell Leukemia

CHAPTER 5

Myelodysplastic/ Myeloproliferative Neoplasms

CHRONIC MYELOMONOCYTIC LEUKEMIA (CMML)

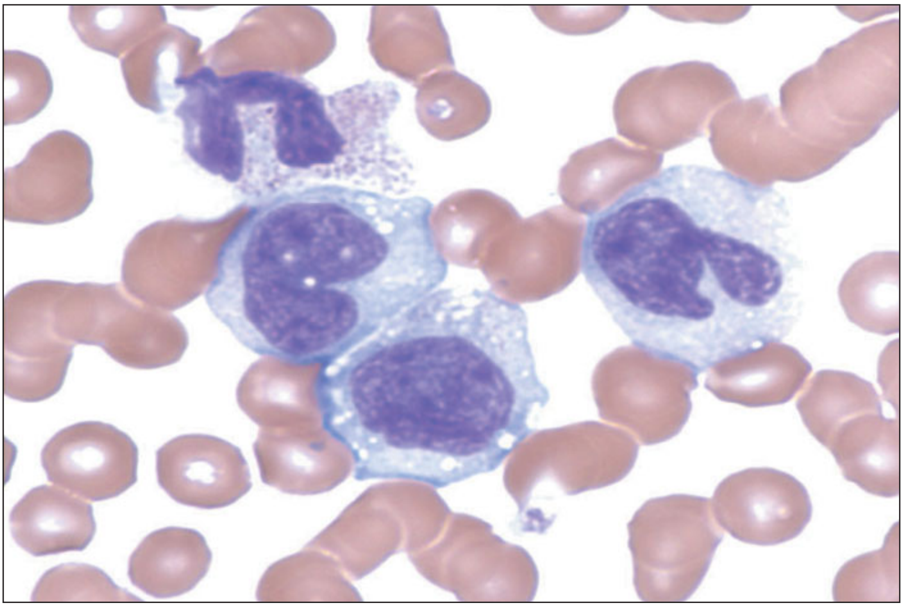


Figure **IIB5-1**

Peripheral blood smear.

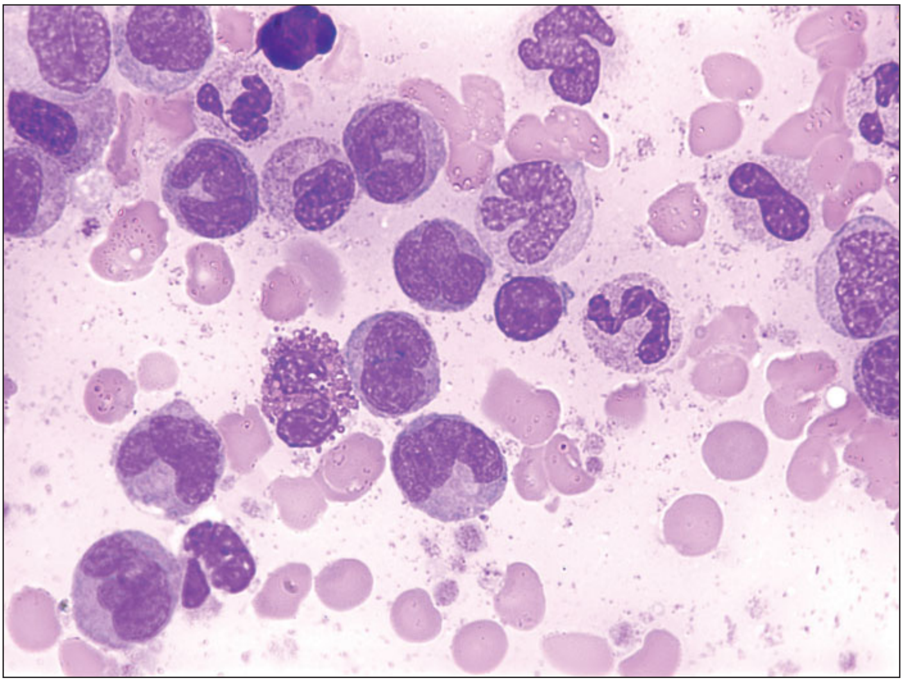


Figure **IIB5-2**

Bone marrow smear.

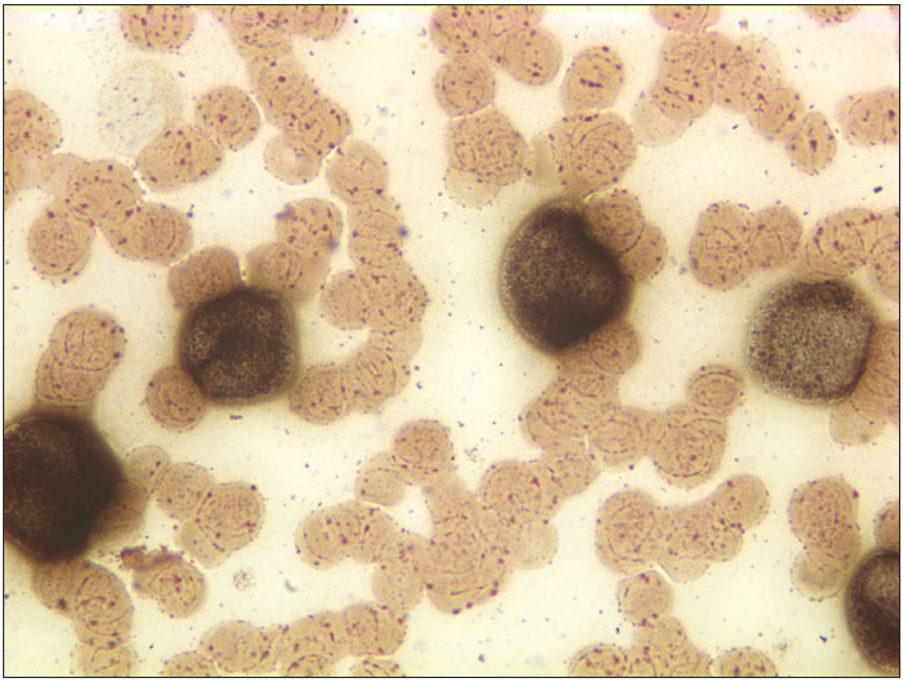


Figure IIB5-3

Nonspecific esterase stain.

Criteria

CMML-1

- Blasts and promonocytes are <5% in the peripheral blood and <10% in the bone marrow

CMML-2

- Blasts and promonocytes are 5–19% in the peripheral blood and 10–19% in the bone marrow or when Auer rods are present

Clinical Features

- Occurs most commonly in persons older than 50 years
- Fatigue and weakness
- Hemorrhagic symptoms
- Infection is the most common cause of death
- Hepatosplenomegaly may be present, especially when the white blood cell count is elevated
- May have skin infiltrations

Pathology

- Expansion of abnormal cells in the bone marrow and a decrease in normal cells
- Clonal malignancy that is characterized by the feature of both a myelodysplastic syndrome and a myeloproliferative neoplasm
- Rearrangements of genetic material may be important in the activation of proto-oncogenes to oncogenes
- Specific abnormalities have not been identified

Laboratory Features

White Blood Cells

- Usually normal to decreased
- Monocytes range from 2 to 5 × 10^9/L but may be above 80 × 10^9/L
- Monocytes are >10% of the leukocytes
- Monocytes are mature but can exhibit abnormal granulation or nuclear lobulation
- Blasts and promonocytes are <20% of the white blood count
- There are <10% neutrophil precursors
- Dysgranulopoiesis is common
- Basophilia is typically mild but rare cases of increased eosinophils have been described

Red Blood Cells

- Anemia is usually normocytic but sometimes macrocytic
- Dimorphic population
- Nucleated red blood cells

Platelets

- Decreased count
- Abnormal forms may be found

Bone Marrow

- Usually hypercellular
- Granulocytic proliferation
- Slight dysgranulopoiesis
- <20% blasts and promonocytes
- Dyserythropoiesis
- Slight dysmegakaryopoiesis

Cytochemistry

- Nonspecific esterase positive
- Myeloperoxidase and Sudan black B negative or weakly positive
- Periodic acid-Schiff negative

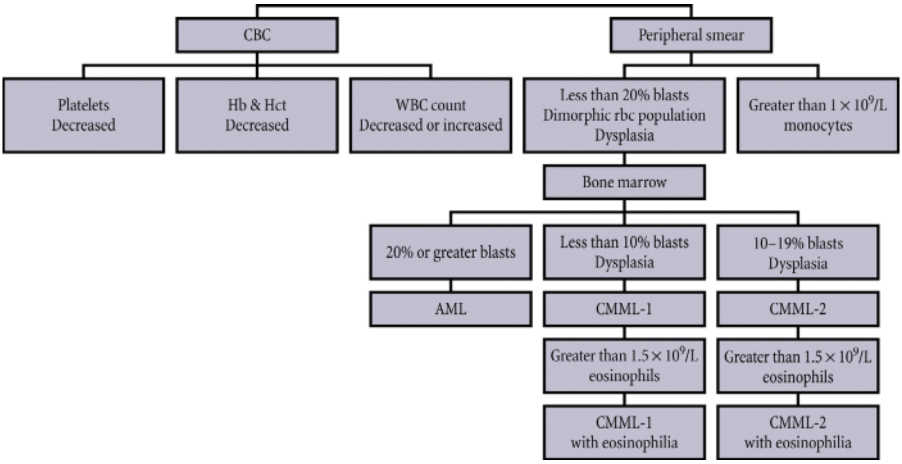
Immunophenotype

- Express the myelomonocytic antigen such as CD33 and CD13
- Variable expression of CD14, CD68, CD64

Genetics

- 20–40% express cytogenetic abnormalities but none is specific
- Frequent abnormalities include +8, −7/del (7q) and structural abnormalities of 12p
- 40% of patients express point mutations of *RAS* genes

Diagnostic Scheme


CBC
Peripheral smear
Platelets Decreased
Hb & Hct Decreased
WBC count Decreased or increased
Less than 20% blasts Dimorphic rbc population Dysplasia
Greater than 1 × 10^9/L monocytes
Bone marrow
20% or greater blasts
Less than 10% blasts Dysplasia
10–19% blasts Dysplasia
AML
CMML-1
CMML-2
Greater than 1.5 × 10^9/L eosinophils
Greater than 1.5 × 10^9/L eosinophils
CMML-1 with eosinophilia
CMML-2 with eosinophilia

ATYPICAL CHRONIC MYELOID LEUKEMIA (aCML), *BCR-ABL2 1* NEGATIVE

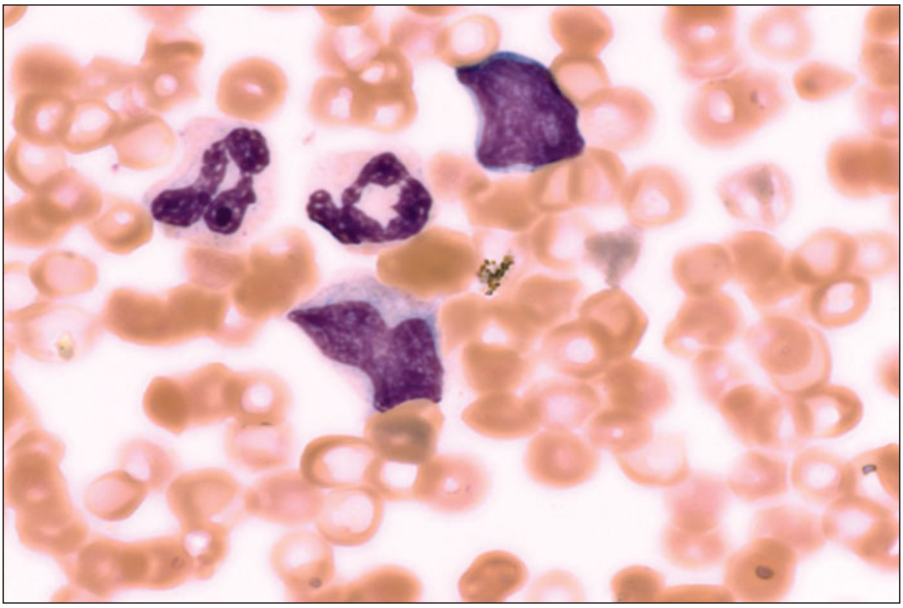


Figure IIB5-4

Peripheral blood smear.

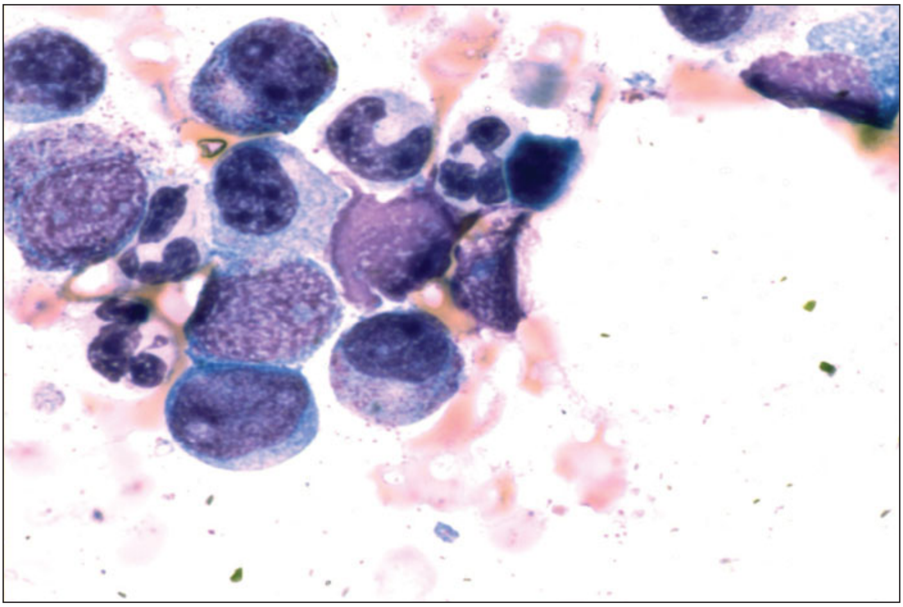


Figure IIB5-5

Bone marrow smear.

Clinical Features

- Occurs in about 1–2% of the chronic myelogenous leukemias
- Patients are usually elderly
- Fatigue, bleeding disorders
- Splenomegaly and hepatomegaly may also be present

Pathology

- Myelodysplastic as well as myeloproliferative features at the time of initial diagnosis
- Principal involvement of the granulocytic line

Laboratory Features

White Blood Cells

- Leukocytosis is variable
- Immature and dysplastic
- The white cell count is $>13 \times 10^9$/L but most have counts from 24 to 96×10^9/L
  - Blasts are usually <5% but must be <20%
  - Promyelocytes, myelocytes, and metamyelocytes comprise about 10–20%
  - Monocytes are usually <10%
  - Basophilia may be observed
  - Dysgranulopoiesis is pronounced
    - Pseudo Pelger-Huët, abnormally clumped chromatin or bizarre segmentation

Red Blood Cells

- Anemia
- Dyserythropoiesis
- Macroovalocytes may be present

Platelets

- Count is variable but decreased numbers are common

Bone Marrow

- Hypercellular due to increased neutrophil and their precursors
- Blasts increased but <20%
- Dysgranulopoiesis
- Variable numbers of megakaryocytes but some dysmegakaryopoiesis is present
- M:E ratios of >10:1 is common
- Some cases have over 30% erythroid precursors and dyserythropoiesis may be seen

Cytochemistry

- Leukocyte alkaline phosphatase level variable

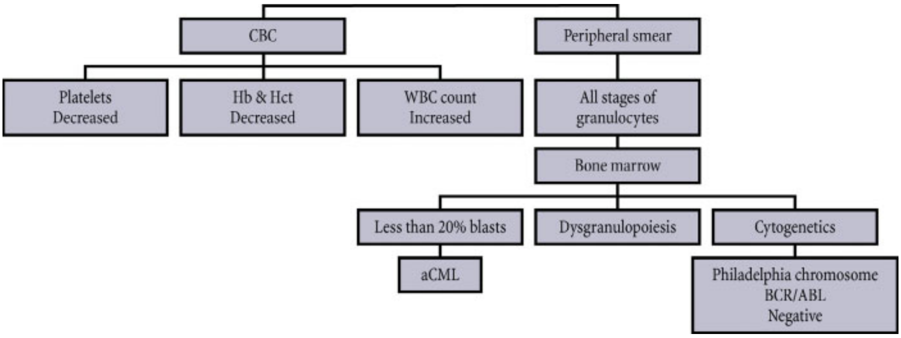
Immunophenotype

- No specific characteristic is seen

Genetics

- Up to 80% of cases have karyotypic abnormalities
- The most common abnormalities include +8 and del (20q)
- There is no *BCR-ABL 1* fusion gene and no rearrangement of *PDGFRA* or *PDGFRB* genes

Diagnostic Scheme


CBC
Peripheral smear
Platelets Decreased
Hb & Hct Decreased
WBC count Increased
All stages of granulocytes
Bone marrow
Less than 20% blasts
Dysgranulopoiesis
Cytogenetics
aCML
Philadelphia chromosome BCR/ABL Negative

JUVENILE MYELOMONOCYTIC LEUKEMIA (JMML)

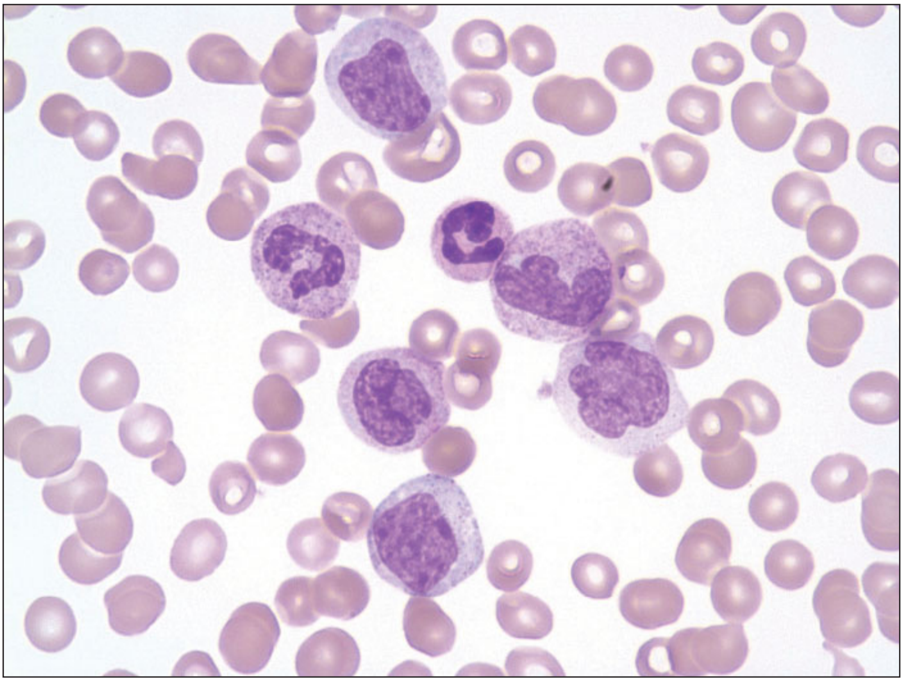


Figure IIB5-6

Peripheral blood smear.

Clinical Features

- Age of onset ranges from 1 month to early adolescence
- 2–3% of all leukemias in children
- 20–30% of all myelodysplastic and myeloproliferative diseases in children
- Approximately 75% of the cases occur in children younger than 3 years
- Malaise, pallor, fever, and recurrent infections
- Skin rashes
- Most patients have infections and hepatosplenomegaly
- Leukemic infiltrates are common in the skin

Pathology

- May be a genetic predisposition
- Exact cause has not been elucidated
- No specific cytogenetic abnormalities

Laboratory Features

White Blood Cells

- White blood count varies from 25 to 30 × 10^9/L
- Mainly neutrophils with some immature cells such as promyelocytes and myelocytes
- Monocytes are increased
- Blasts and promonocytes usually account for less than 5% and always less than 20%

Red Blood Cells

- Nucleated red blood cells are frequent
- Marked increase in HbF

Platelets

- Variable but may be decreased and may be severe

Bone Marrow

- Hypercellular
- Granulocytic proliferation but rarely erythroid precursors can predominate
- Monocytes account for about 5–10% of cells
- Blasts and promonocytes are <20%
- No Auer rods
- Dysplasias are minimal but pseudo Pelger-Huët or hypogranular forms may be seen
- Megakaryocytes are often decreased

Cytochemistry

- Nonspecific esterase positive in monocytic precursors

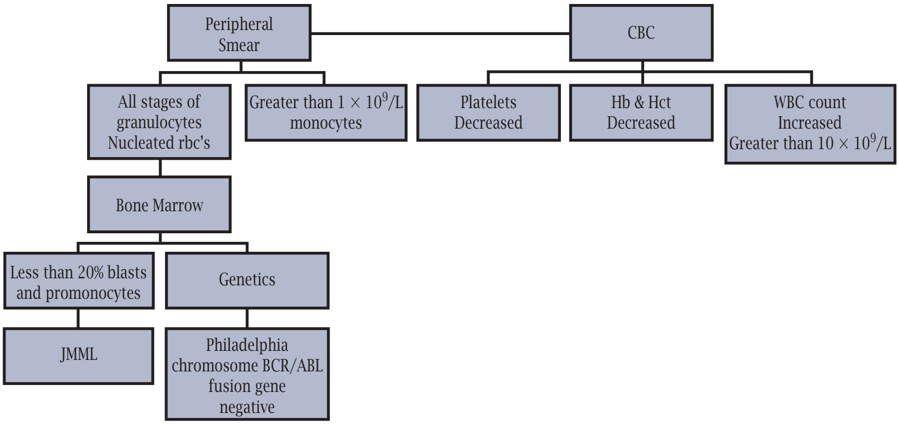
Immunophenotype

- No specific immunophenotypic abnormalities have been reported

Genetics

- 25% of cases have monosomy 7
- 65% have a normal karyotype
- Philadelphia chromosome and *BCR-ABL 1* fusion gene are absent

Diagnostic Scheme


Peripheral Smear
CBC
All stages of granulocytes Nucleated rbc's
Greater than 1 × 10^9/L monocytes
Platelets Decreased
Hb & Hct Decreased
WBC count Increased Greater than 10 × 10^9/L
Bone Marrow
Less than 20% blasts and promonocytes
Genetics
JMML
Philadelphia chromosome BCR/ABL fusion gene negative

CHAPTER 6

Myelodysplastic Syndromes/Neoplasms (MDS)

REFRACTORY CYTOPENIA WITH UNILINEAGE DYSPLASIA (RCUD)

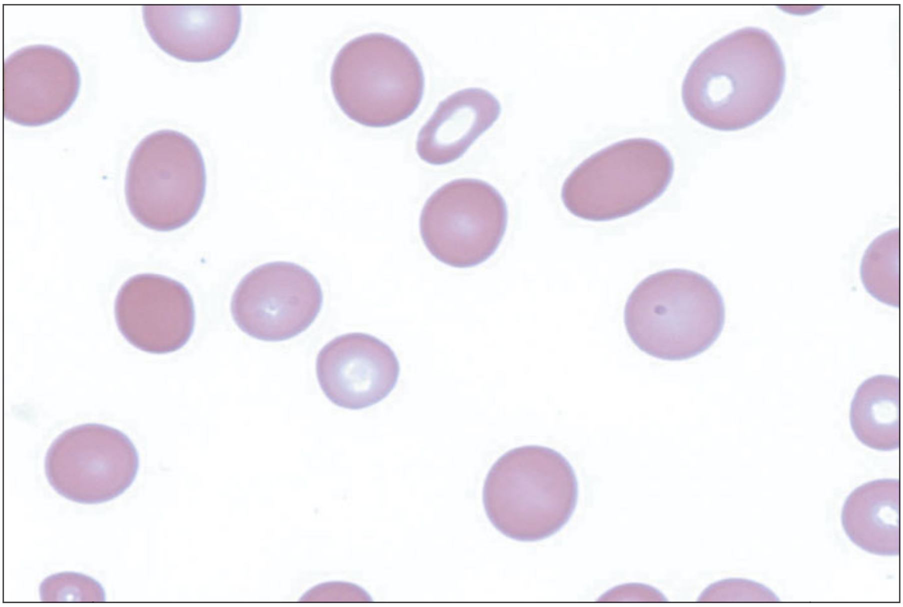


Figure IIB6-1

Peripheral blood smear.

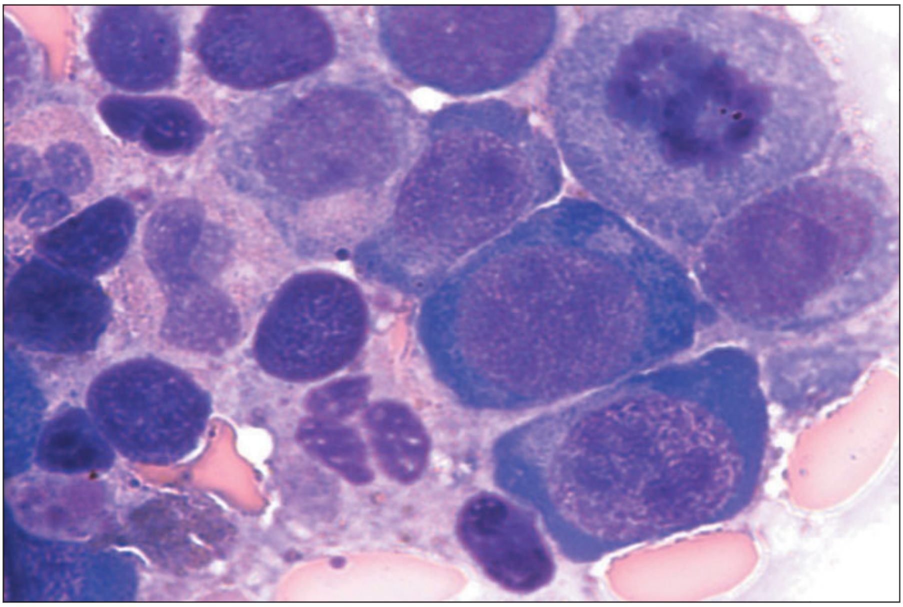


Figure IIB6-2

Bone marrow smear.

Refractory Anemia (RA)

Clinical Features

- Usually occurs in adults over 50 years of age
- Pallor and fatigue
- Asymptomatic if early in the disease

Pathology

- Usually occurs in adults over 50 years of age
- RCUD accounts for about 10–20% of the cases of MDS

Laboratory Features

White Blood Cells

- Normal count
- <1% blasts

Red Blood Cells

- Normocytic/normochromic or macrocytic/normochromic anemia
- Oval macrocytes
- Dimorphic population
- Increased mean corpuscular volume
- Increased red blood cell distribution width

Platelets

- Normal count

Bone Marrow

- <5% blasts
- <15% ringed sideroblasts
- Cellularity normal or increased
- Erythrocytic hyperplasia with dysplasia

Cytochemistry

- Prussian blue stain with less than 15% ring sideroblasts

Immunophenotype

- Aberrant features of erythroid precursors can be seen

Genetics

- 50% of cases have abnormalities but not specific ones

Chemistries

- Normal to increased iron level

Refractory Neutropenia (RN)

Laboratory Features

White Blood Cells

- >10% dysplastic neutrophils
- Nuclear hypolobulation and hypogranularity

Bone Marrow

- >10% dysplastic neutrophils

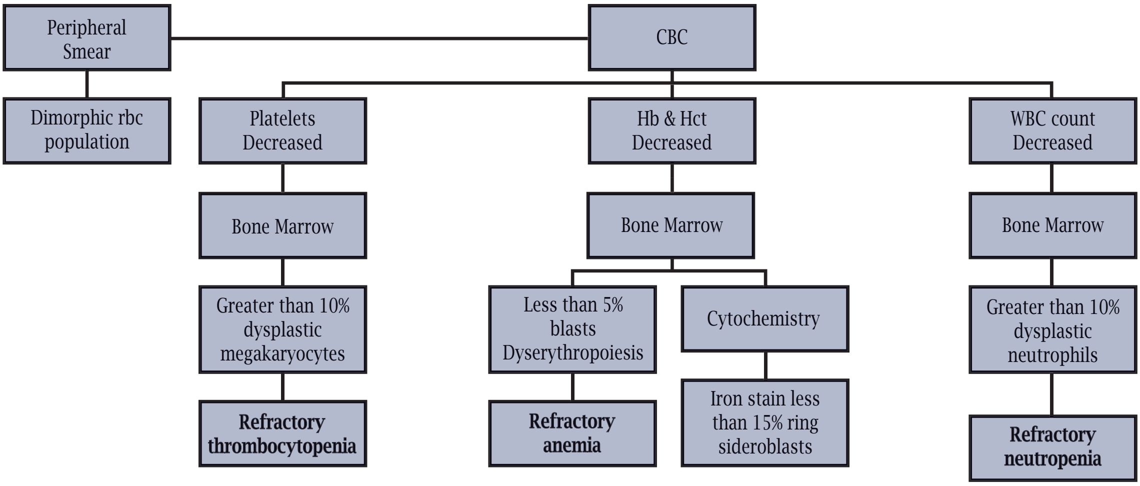
Refractory Thrombocytopenia (RT)

Laboratory Features

Bone Marrow

- >10% dysplastic megakaryocytes (of at least 30 megakaryocytes)
- Vacuolated, hypolobulated, binucleated and micromegakaryocytes are common
- Megakaryocyte numbers may be decreased or increased
- <10% of the other myeloid cell lines are dysplastic

Diagnostic Scheme


Peripheral Smear
CBC
Dimorphic rbc population
Platelets Decreased
Hb & Hct Decreased
WBC count Decreased
Bone Marrow
Bone Marrow
Bone Marrow
Greater than 10% dysplastic megakaryocytes
Less than 5% blasts Dyserythropoiesis
Cytochemistry
Greater than 10% dysplastic neutrophils
Refractory thrombocytopenia
Refractory anemia
Iron stain less than 15% ring sideroblasts
Refractory neutropenia

REFRACTORY ANEMIA WITH RING SIDEROBLASTS (RARS)

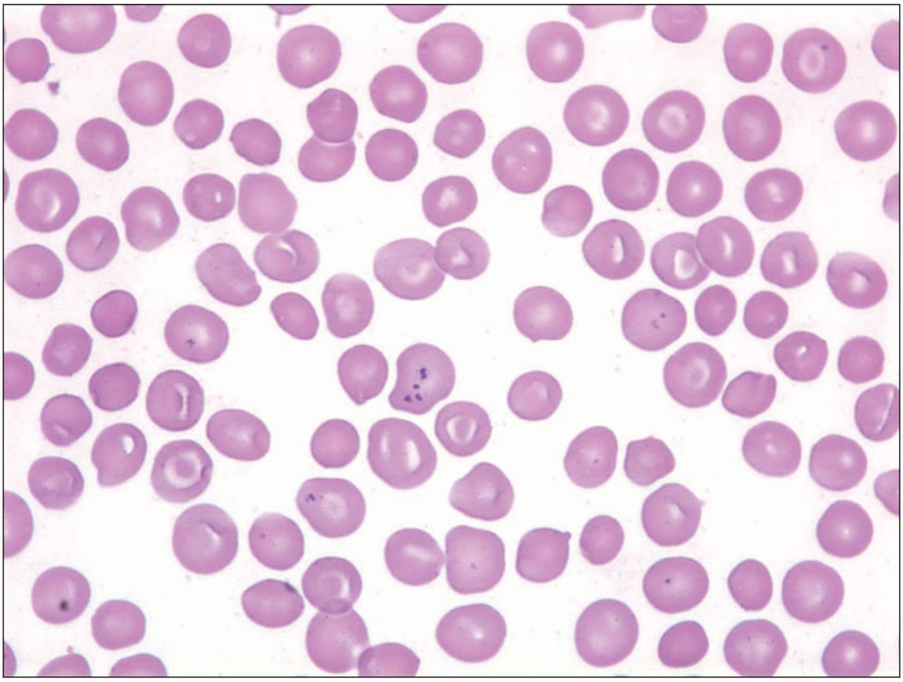


Figure IIB6-3

Peripheral blood smear.

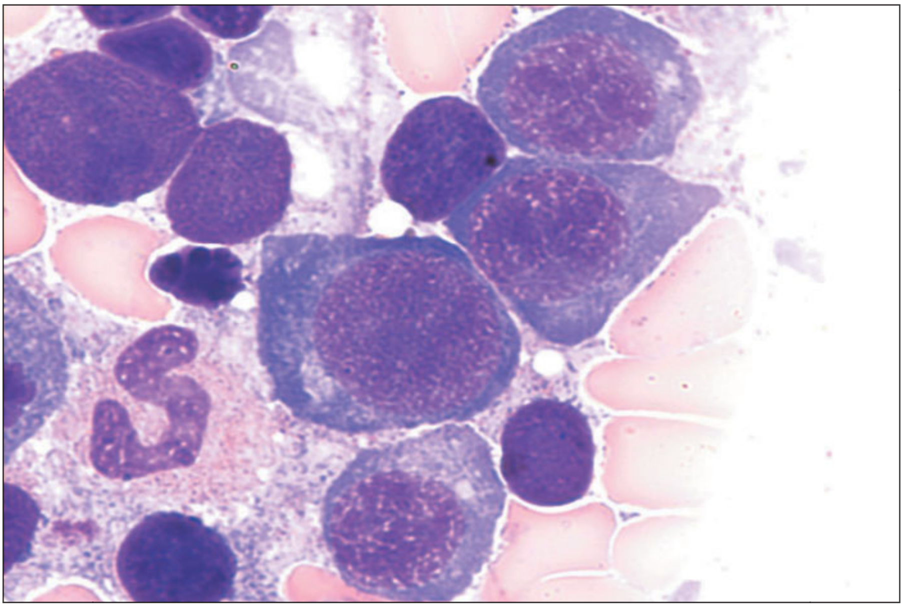


Figure IIB6-4

Bone marrow smear.

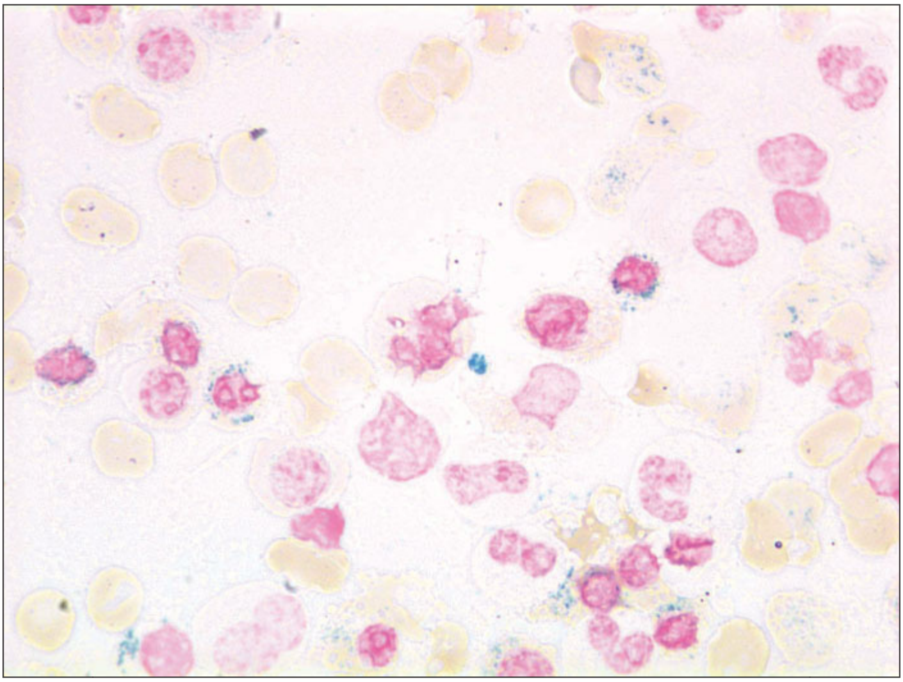


Figure **IIB6-5**

Prussian blue stain.

Clinical Features

- Also known as idiopathic acquired sideroblastic anemia or sideroblastic anemia
- Fatigue and pallor
- Liver and spleen may show evidence of iron deposition

Pathology

- Accounts for 3–11% of MDS cases
- Usually occurs in adults over 50 years of age
- More frequent in males than females

Laboratory Features

White Blood Cells

- <1% blasts
- Normal count

Red Blood Cells

- Normochromic, macrocytic or normochromic, normocytic anemia
- Dimorphic pattern with hypochromic microcytes and normocytic or macrocytic cells
- Occasional Pappenheimer bodies
- Decreased reticulocyte count

Platelets

- Normal count

Bone Marrow

- <5% blasts
- Dyserythropoiesis (>10% of all nucleated red blood cells)
- ≥15% ringed sideroblasts

Cytochemistry

- 15% or more of the red cell precursors are ringed sideroblasts (5 or more iron granules encircling one-third or more of the nucleus)

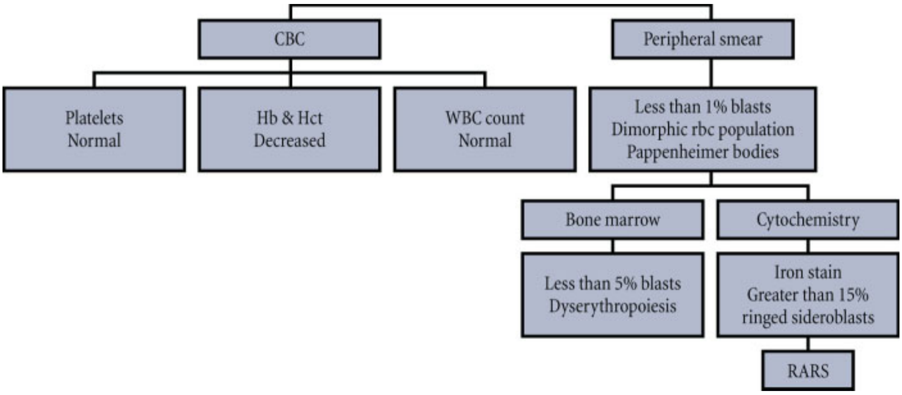
Immunophenotype

- Aberrant features of the erythropoietic precursors may be seen

Genetics

- 5–20% of cases involve a clonal chromosomal abnormality most involving single chromosome abnormality

Diagnostic Scheme


CBC
Peripheral smear
Platelets Normal
Hb & Hct Decreased
WBC count Normal
Less than 1% blasts
Dimorphic rbc population
Pappenheimer bodies
Bone marrow
Cytochemistry
Less than 5% blasts
Dyserythropoiesis
Iron stain
Greater than 15%
ringed sideroblasts
RARS

REFRACTORY CYTOPENIA WITH MULTILINEAGE DYSPLASIA (RCMD)

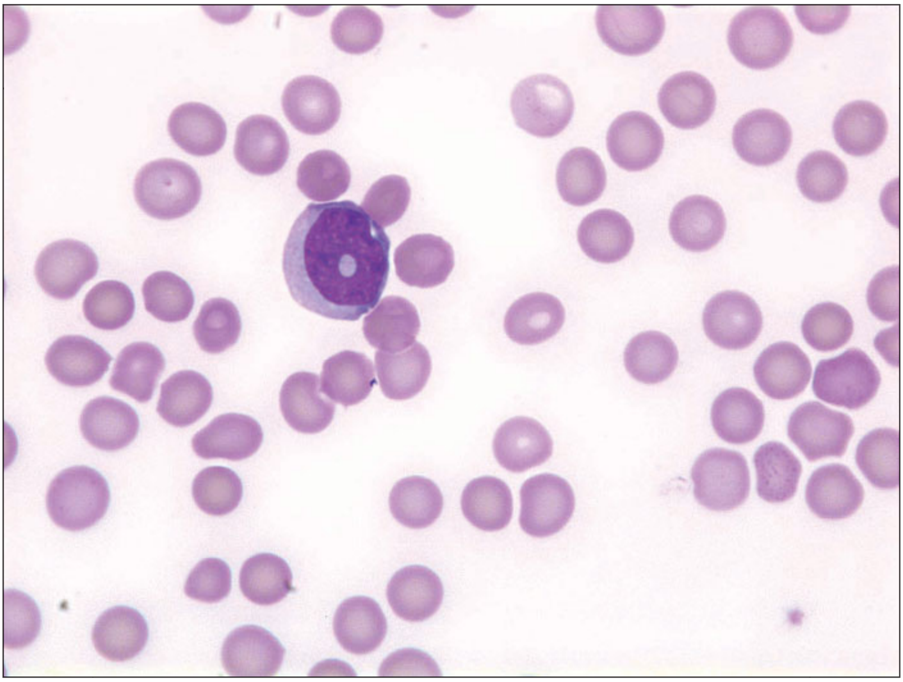


Figure IIB6-6

Peripheral blood smear.

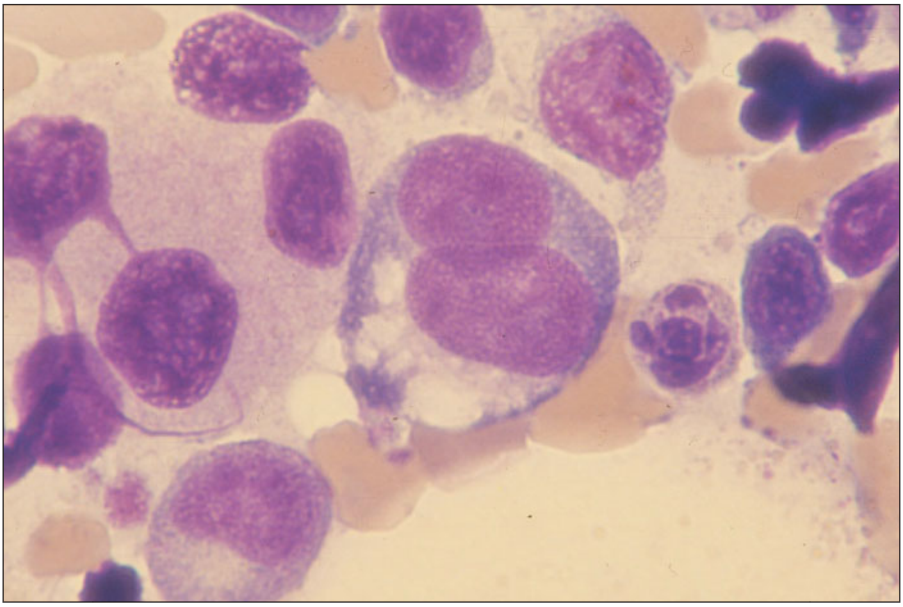


Figure IIB6-7

Bone marrow smear.

Clinical Features

- Patients present with symptoms of bone marrow failure with cytopenia in two or more myeloid lineages
  - Pallor
  - Infections
  - Bleeding

Pathology

- Usually occurs in adults over 50 years of age
- Slight predominance of males
- Accounts for about 30% of cases of MDS

Laboratory Features

White Blood Cells

- Hypogranulation of neutrophils
- Pseudo-Pelger–Huët nuclei
- No or rare blasts
- No Auer rods
- $<1 \times 10^9$/L monocytes

Red Blood Cells

- Decreased
- Dimorphic population

Platelets

- Normal to decreased
- May have abnormal morphology

Bone Marrow

- Dysplasia is ≥10% of the cells in two or more myeloid cell lines
- <5% blasts
- No Auer rods

Cytochemistry

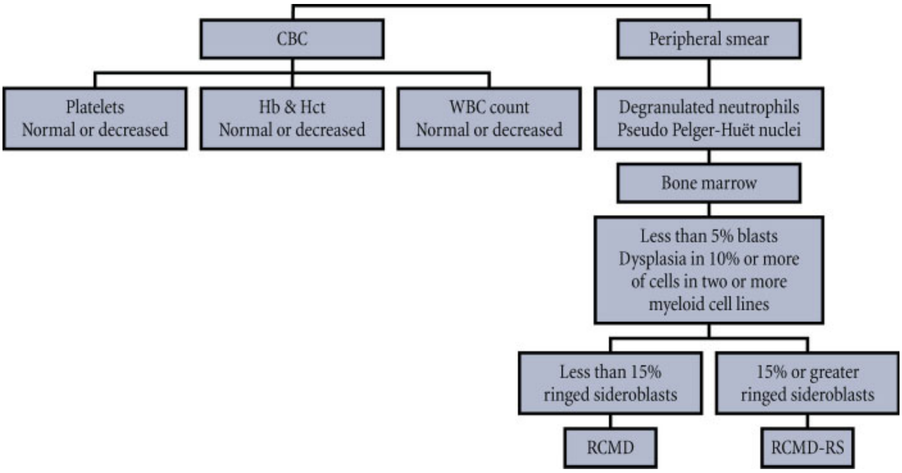
Prussian Blue Stain

- <15% ringed sideroblasts indicate refractory cytopenia with multilineage dysplasia
- ≥15% ringed sideroblasts indicate refractory cytopenia with multilineage dysplasia with ringed sideroblasts

Genetics

- Abnormalities include trisomy 8, monosomy 7, del(7q), monosomy 5, del(5q), and del(20q)

Diagnostic Scheme


CBC
Peripheral smear
Platelets Normal or decreased
Hb & Hct Normal or decreased
WBC count Normal or decreased
Degranulated neutrophils Pseudo Pelger-Huët nuclei
Bone marrow
Less than 5% blasts Dysplasia in 10% or more of cells in two or more myeloid cell lines
Less than 15% ringed sideroblasts
15% or greater ringed sideroblasts
RCMD
RCMD-RS

REFRACTORY ANEMIA WITH EXCESS BLASTS (RAEB)

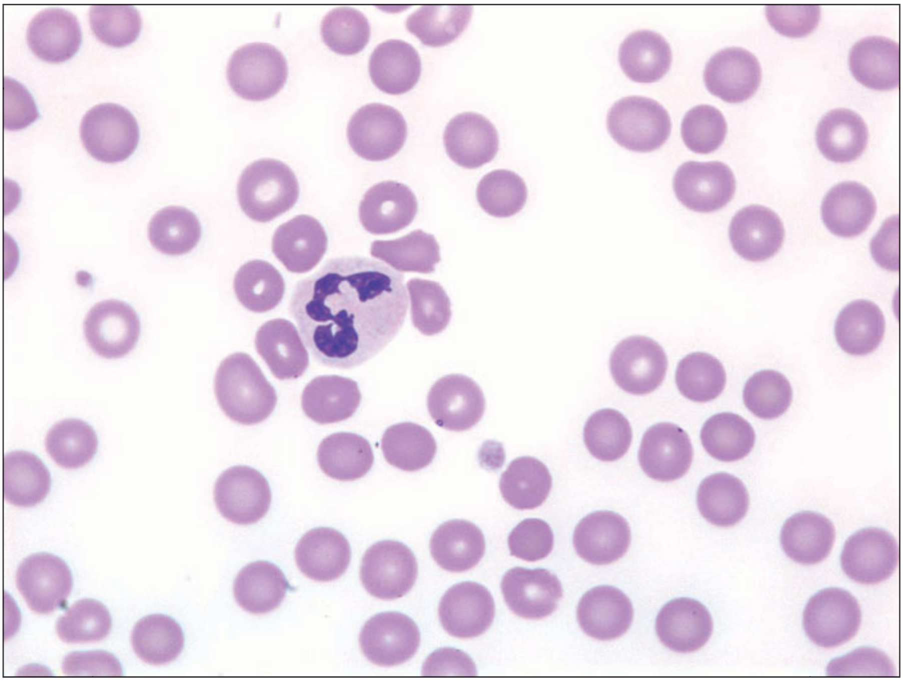


Figure IIB6-8

Peripheral blood smear. RAEB-1.

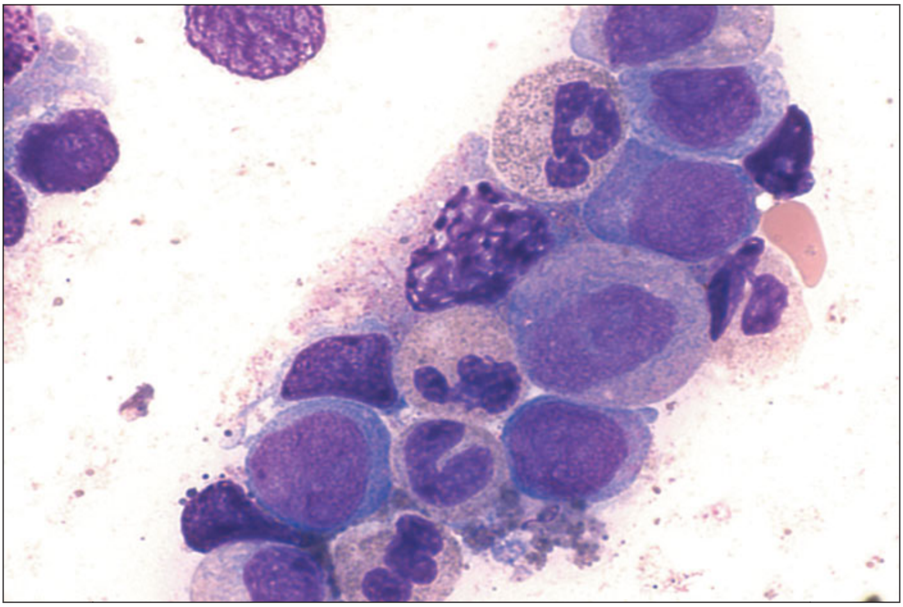


Figure IIB6-9

Bone marrow smear. RAEB-1.

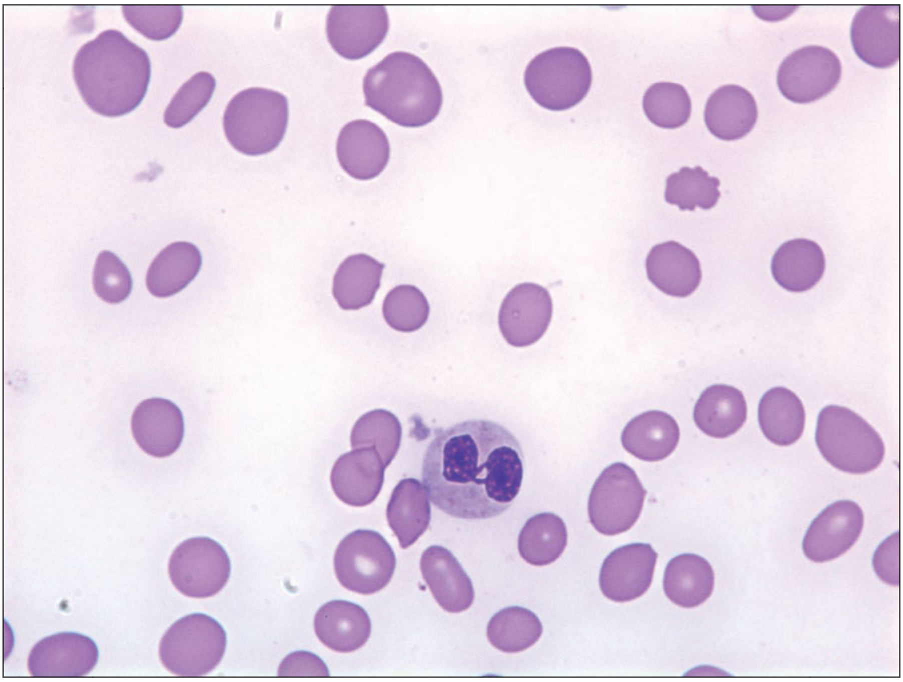


Figure **IIB6-10**

Peripheral blood smear. RAEB-2.

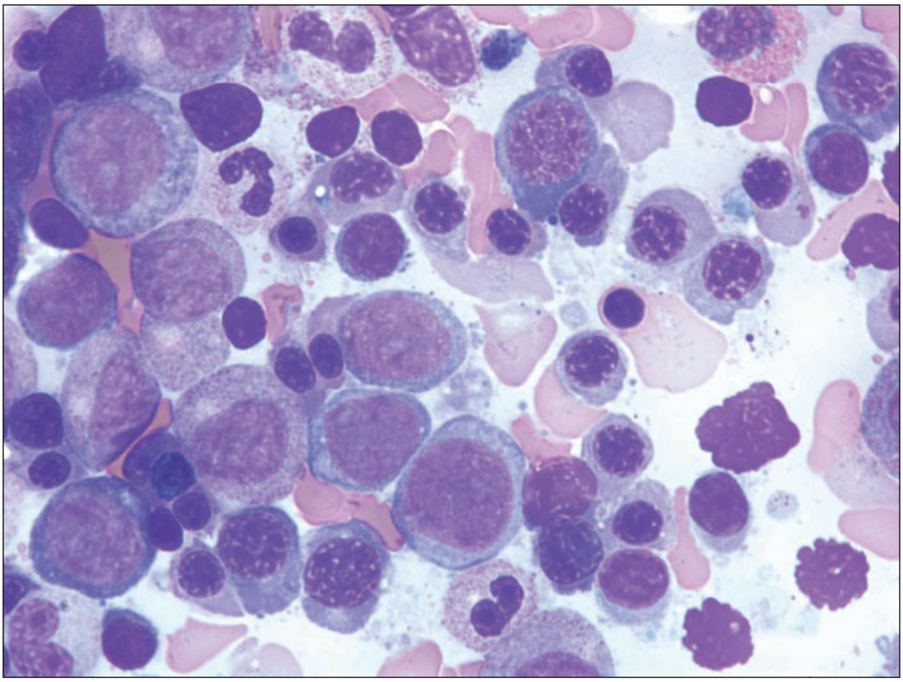


Figure **IIB6-11**

Bone marrow smear. RAEB-2.

Clinical Features

- Fatigue and weakness
- Hemorrhagic symptoms
- Infection is the most common cause of death
- Hepatomegaly and splenomegaly may be present

Pathology

- Occurs most commonly in older adults
- Etiology is unknown

Laboratory Features

RAEB-1

White Blood Cells

- Neutropenia
- Degranulated neutrophils
- Pseudo-Pelger–Huët cells
- <1 × 10^9/L monocytes
- <5% blasts

Red Blood Cells

- Anisopoikilocytosis with macrocytes
- Dimorphic population
- Decreased reticulocytes

Bone Marrow

- Hypercellular, may be hypocellular or normocellular
- Dysgranulopoiesis and/or dyserythropoiesis and/or dysmegakaryopoiesis
- May have increased number of ringed sideroblasts
- 5–9% blasts
- No Auer rods

RAEB-2

White Blood Cells

- Neutropenia
- Degranulated neutrophils
- Pseudo-Pelger–Huët cells
- <1 × 10^9/L monocytes
- 5–19% blasts
- Auer rods may be seen

Red Blood Cells

- Anisopoikilocytosis with macrocytes
- Decreased reticulocyte count

Platelets

- Decreased
- Large with abnormal morphology

Bone Marrow

- Hypercellular, may be hypocellular or normocellular
- Dysgranulopoesis and/or dyserythropoiesis and/or dysmegakaryopoiesis
- May have increased number of ringed sideroblasts
- 10–19% blasts
- Auer rods may be seen

Cytochemistry

- Decreased activity of peroxidase and Sudan black B if cells are degranulated
- Prussian blue stain may show increased number of ringed sideroblasts

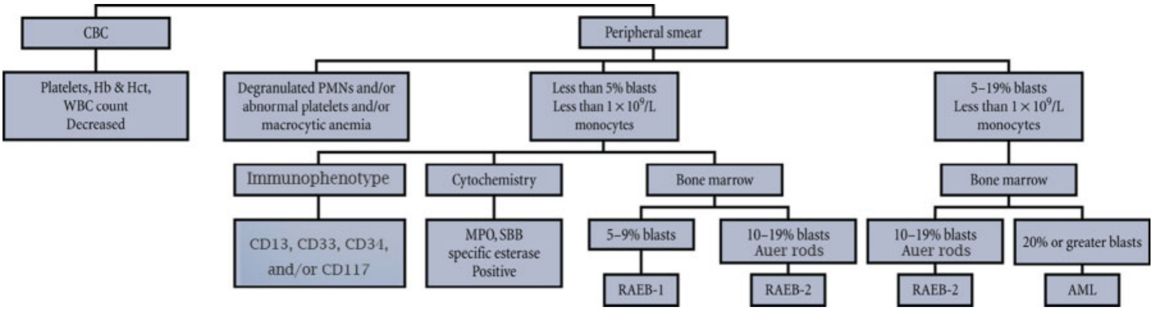
Immunophenotype

- CD13, CD33, CD34, and/or CD117 positive

Genetics

- 30–50% of cases have clonal cytogenetic abnormalities and can include +8, −5, del(5q), −7, del(7q), and del(20q)

Diagnostic Scheme


CBC
Peripheral smear
Platelets, Hb & Hct, WBC count Decreased
Degranulated PMNs and/or abnormal platelets and/or macrocytic anemia
Less than 5% blasts Less than 1 × 10⁹/L monocytes
5–19% blasts Less than 1 × 10⁹/L monocytes
Immunophenotype
Cytochemistry
Bone marrow
Bone marrow
CD13, CD33, CD34, and/or CD117
MPO, SBB specific esterase Positive
5–9% blasts
10–19% blasts Auer rods
10–19% blasts Auer rods
20% or greater blasts
RAEB-1
RAEB-2
RAEB-2
AML

MYELODYSPLASTIC SYNDROME WITH ISOLATED DEL(5q)

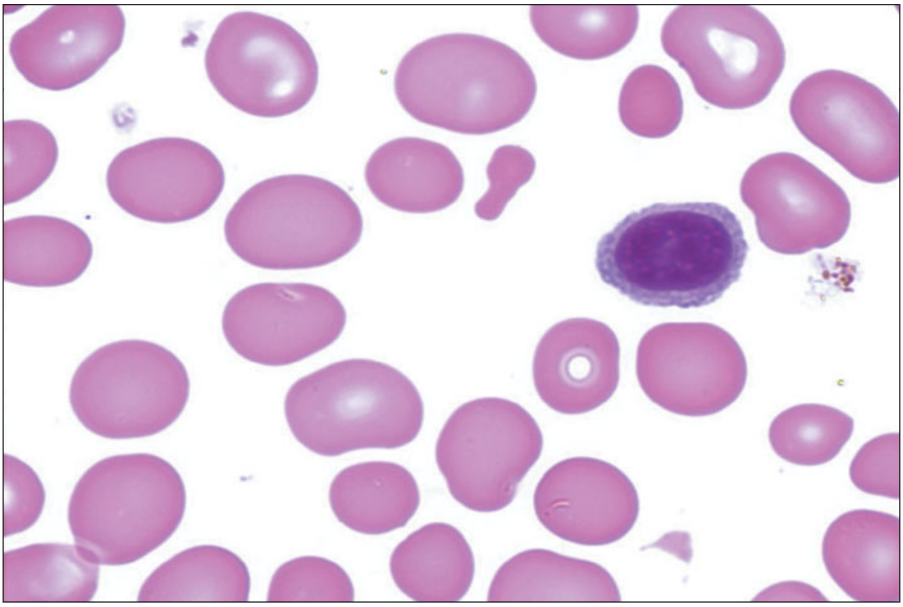


Figure IIB6-12

Peripheral blood smear.

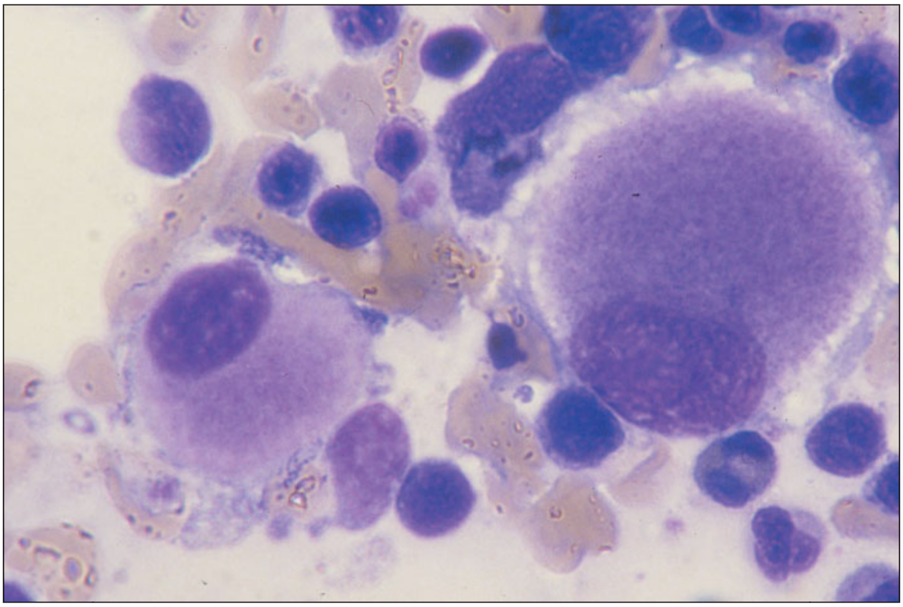


Figure IIB6-13

Bone marrow smear.

Clinical Features

- Also known as 5q- syndrome
- Symptoms progress from anemia to hemorrhage and infection
- Fatigue and weakness may be the presenting symptoms

Pathology

- Usually occurs in older females
- Loss of a portion of the long arm of chromosome 5
- Loss of genes for growth factors

Laboratory Features

White Blood Cells

- Count decreased
- Neutropenia
- <5% blasts

Red Blood Cells

- Macrocytic anemia
- Hemoglobin level often <8.0 g/dL

Platelets

- Normal or increased

Bone Marrow

- <5% blasts
- Hypolobulated megakaryocytes
- Hypercellular or normocellular
- Increased megakaryocytes

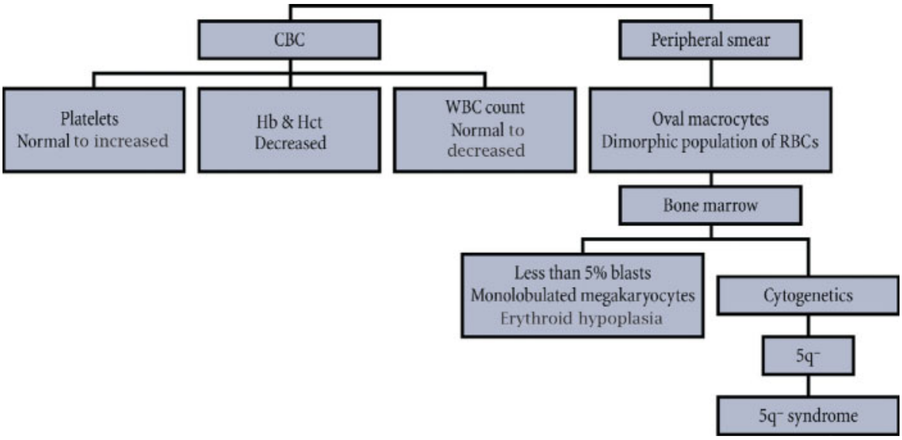
Cytochemistry

- Prussian blue stain
  - <15% ringed sideroblasts

Genetics

- Deletion of bands q31–q33 on the long arm of chromosome 5

Diagnostic Scheme


CBC
Peripheral smear
Platelets Normal to increased
Hb & Hct Decreased
WBC count Normal to decreased
Oval macrocytes Dimorphic population of RBCs
Bone marrow
Less than 5% blasts Monolobulated megakaryocytes Erythroid hypoplasia
Cytogenetics
5q⁻
5q⁻ syndrome

CHAPTER 7

Acute Myeloid Leukemia (AML) and Related Precursor Neoplasms

ACUTE MYELOID LEUKEMIA (AML) WITH RECURRENT GENETIC ABNORMALITIES

AML with t(8;21)(q22; q22); *RUNX1-RUNX1T1*

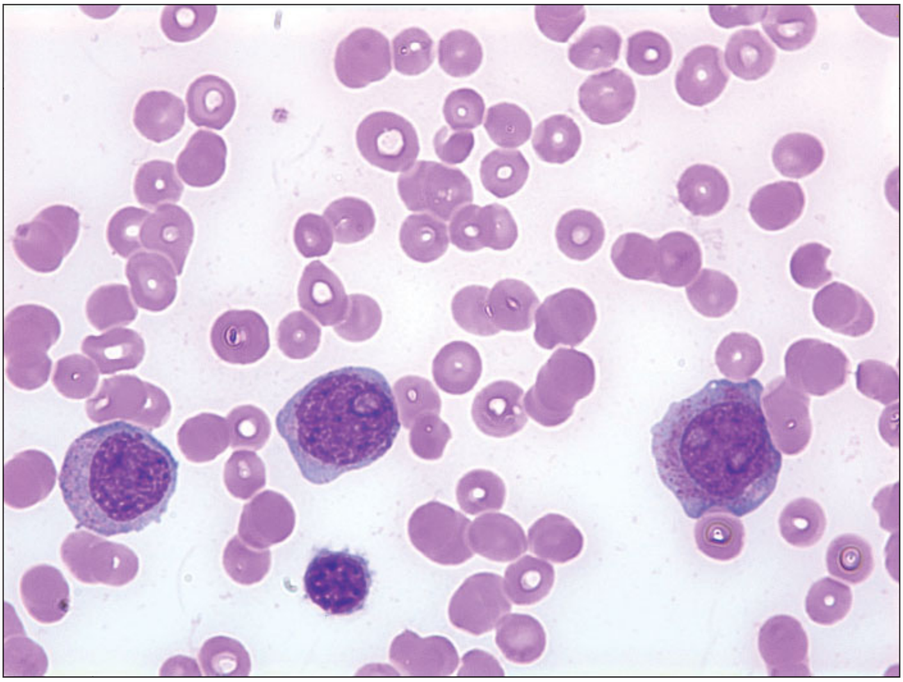


Figure **IIB7-1**

Peripheral blood smear.

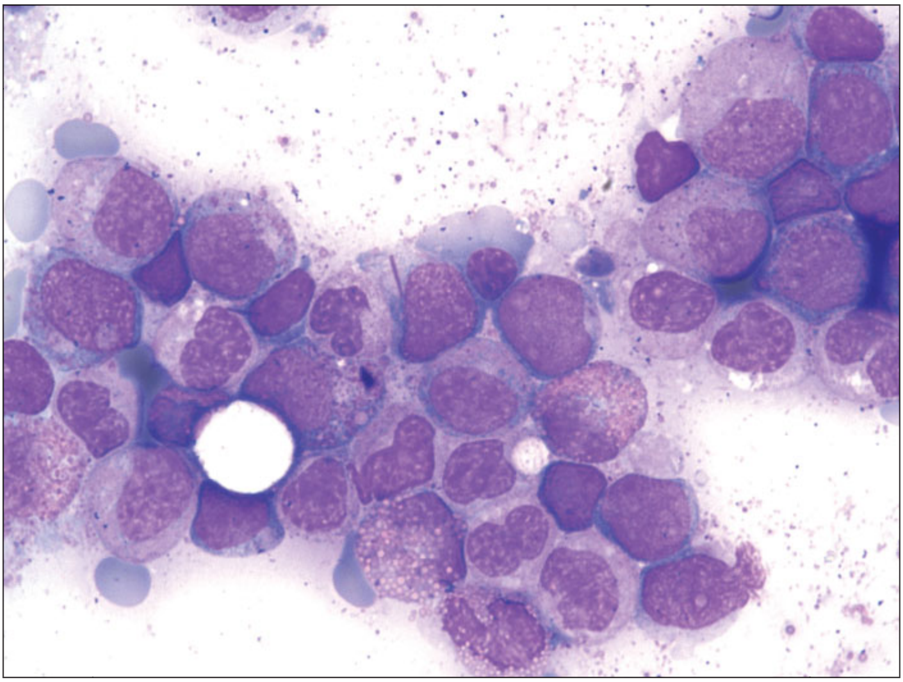


Figure **IIB7-2**

Bone marrow smear.

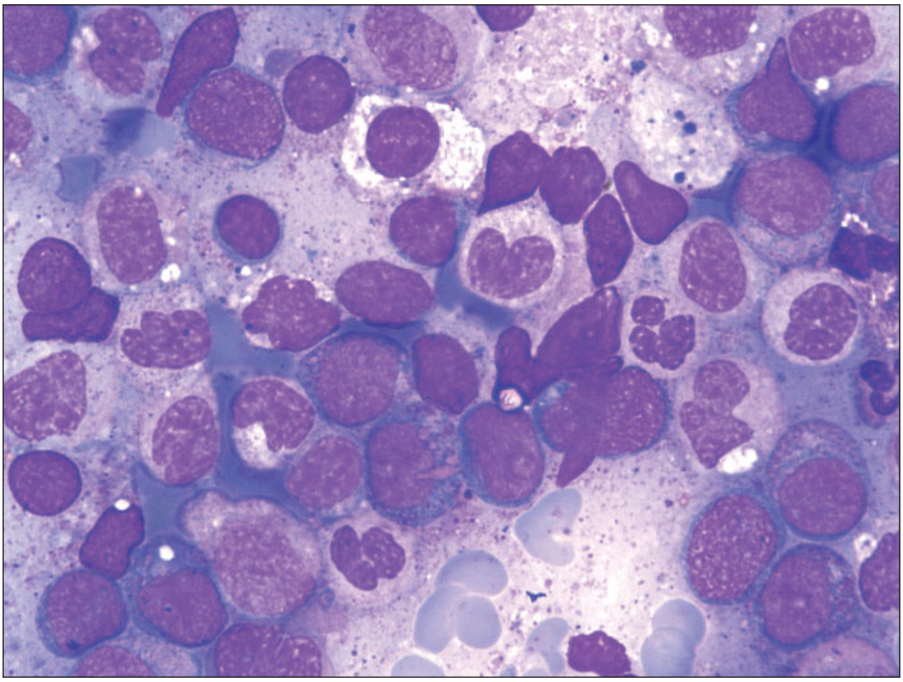


Figure IIB7-3

Bone marrow smear.

Clinical Features

- Myeloid sarcomas may be present at the time of diagnosis
- Weakness and pallor associated with anemia
- Bleeding due to decreased platelet count
- Infection if neutropenia exists

Pathology

- Occurs predominantly in younger people
- Accounts for about 5% of the AML cases
- Shows maturation in the neutrophilic lineage
- Disruption of the core binding factor
- Previously known as *AML1*

Laboratory Features

White Blood Cells

- Large blasts with abundant basophilic cytoplasm
- Smaller blasts may be present
- Auer rods are common with abnormally long pointed ends
- Granular myeloblasts may be the predominant cell

Red Blood Cells

- Anemia may be present

Platelets

- May be decreased

Bone Marrow

- If the 8;21 translocation is present, may have <20% blasts for a diagnosis
- Some blasts may show pseudo-Chédiak-Higashi granules
- Auer rods are frequently found
- Granulocytic series show variable dysplasia
- Eosinophil precursors are frequently increased but don't have cytoplasmic abnormalities
- Monocytic component is minimal or absent

Cytochemistry

- Myeloperoxidase positive

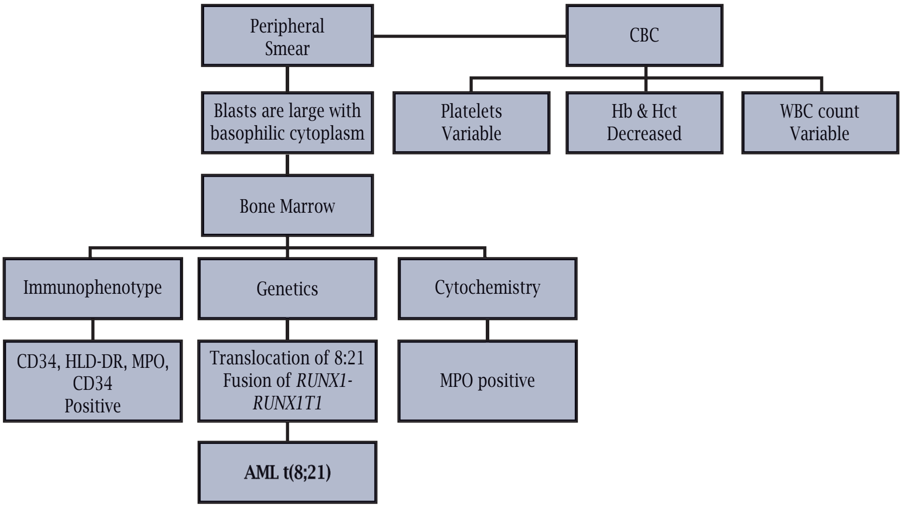
Immunophenotype

- Strong expression of CD34
- Will also show CD13, MPO, and HLA-DR
- If CD56 is present, it indicates a poorer prognosis

Genetics

- Balanced abnormalities of t(8;21)(q22;q22)
- Translocations result in a fusion of *RUNX1-RUNX1T1*
- Additional chromosomal abnormalities can be seen in approximately 70% of the cases

Diagnostic Scheme


Peripheral Smear
CBC
Blasts are large with basophilic cytoplasm
Platelets Variable
Hb & Hct Decreased
WBC count Variable
Bone Marrow
Immunophenotype
Genetics
Cytochemistry
CD34, HLD-DR, MPO, CD34 Positive
Translocation of 8:21 Fusion of RUNX1-RUNX1T1
MPO positive
AML t(8;21)

AML with inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*

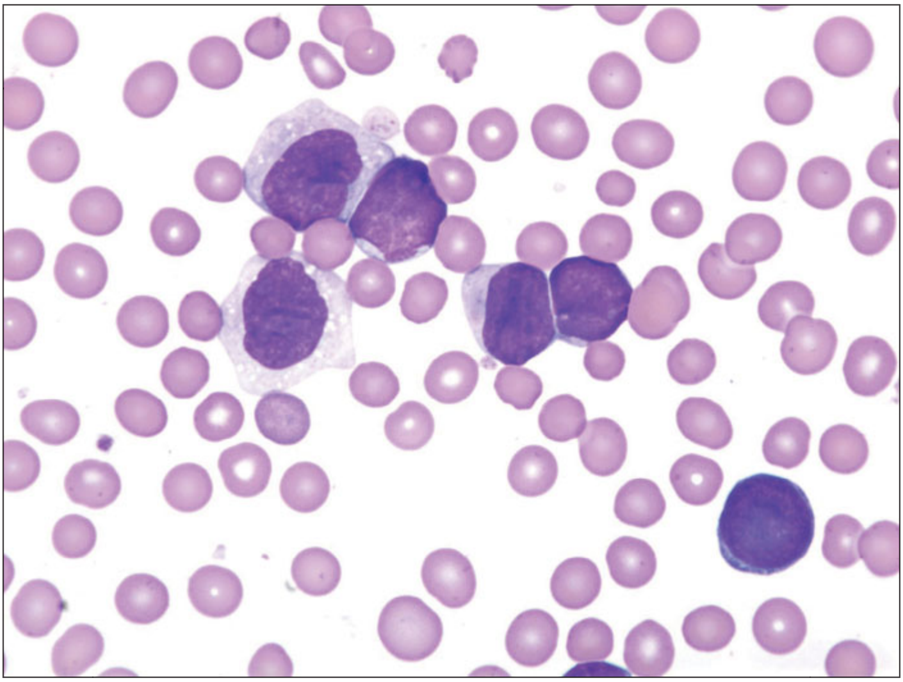


Figure IIB7-4

Peripheral blood smear.

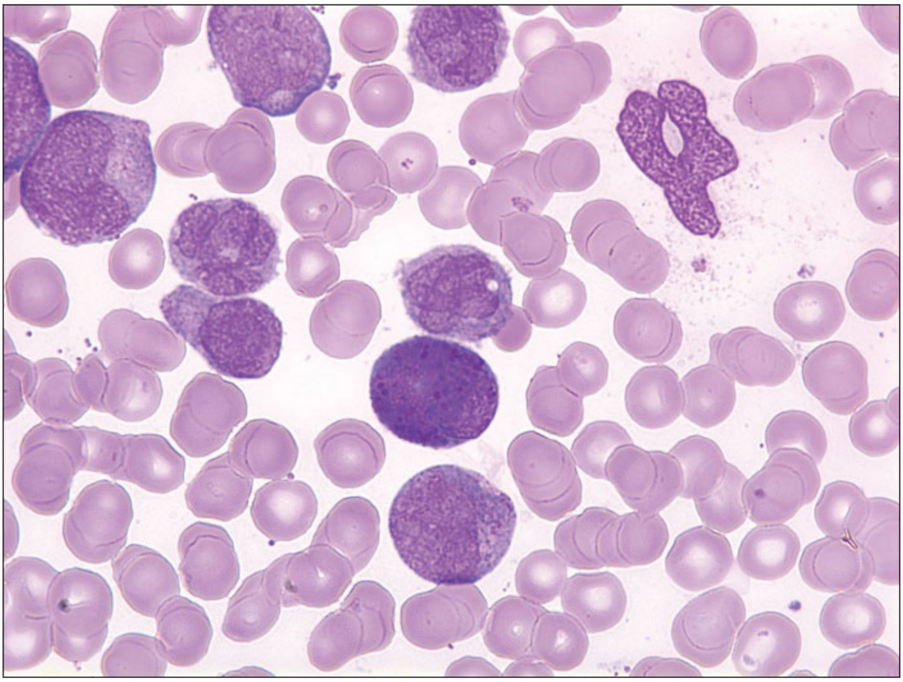


Figure IIB7-5

Bone marrow smear.

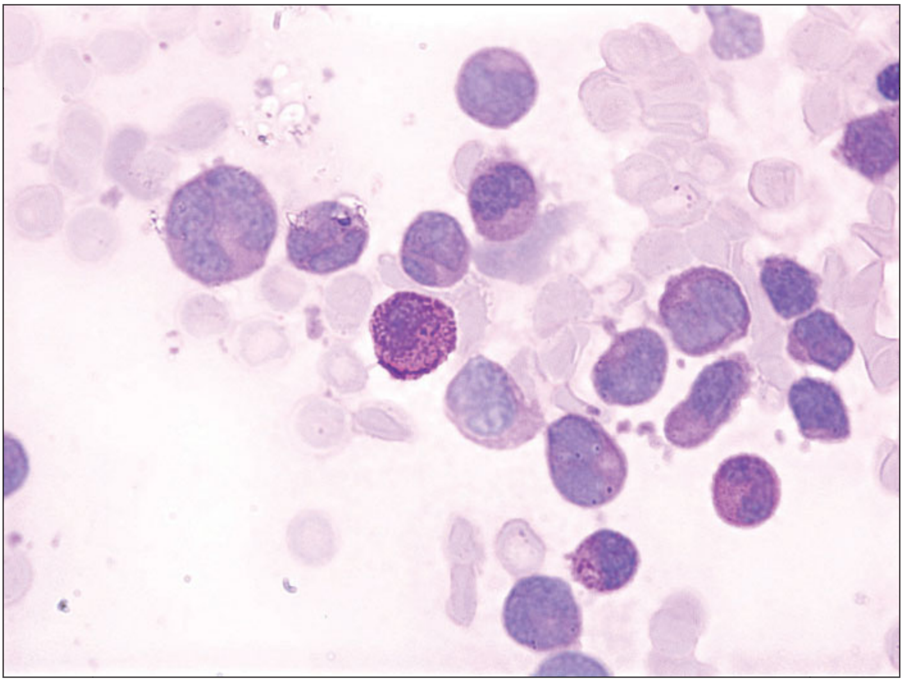


Figure IIB7-6

Periodic acid-Schiff stain.

Clinical Features

- Occurs at all age groups but more likely in younger patients
- Myeloid sarcomas may be present
- Pallor, fatigues, and weakness from anemia
- Bleeding, bruising, and petechial hemorrhages caused by thrombocytopenia
- Bone tenderness, hepatosplenomegaly, and lymphadenopathy

Pathology

- Found in about 5–8% of all patients with AML
- Shows acute myelomonocytic leukemia
- Exhibits an abnormal eosinophilic component in the bone marrow

Laboratory Features

White Blood Cells

- Increased count
- Monoblasts, promonocytes, and myeloblasts can be seen

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- Predominant myelomonocytic and eosinophilic component
- Decreased number of mature neutrophils
- Variable number of eosinophils but usually increased and at all stages of maturation
- Eosinophilic granules are larger than normal and have an intense purple-violet color
- Auer rods may be seen in myeloblasts

Cytochemistry

- Naphthol-ASD-chloroacetate esterase is positive in the abnormal eosinophils
- Periodic acid-Schiff is positive in the abnormal eosinophils
- Myeloblasts are myeloperoxidase positive
- Monoblasts and promonocytes usually show nonspecific esterase positive

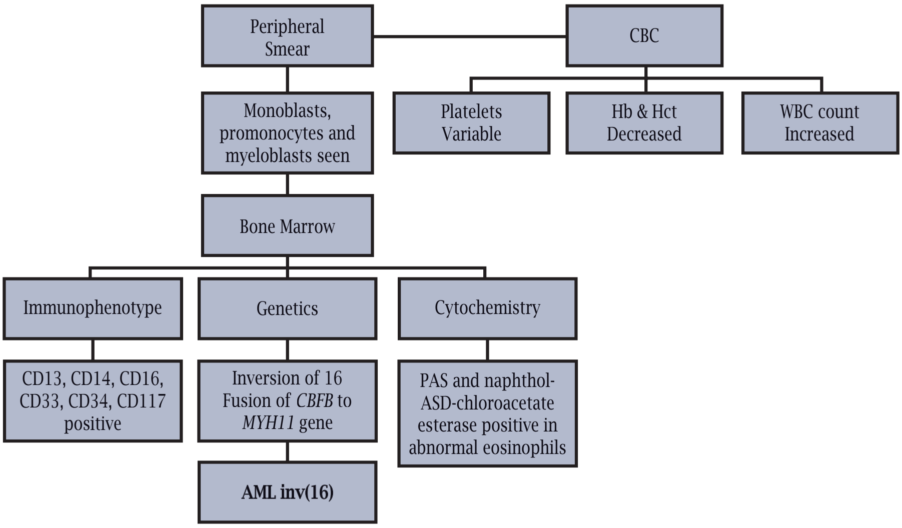
Immunophenotype

- Complex with the presence of multiple blast populations
- High CD34 and CD117 expression
- CD13, CD33, and CD15 also found
- CD4, CD11b, CD11c, CD14, CD64, and CD36 also express monocytic components

Genetics

- Inv(16)(p13.1;q22) found in the majority of cases
- Abnormal genetics rearrangements result in the fusion of the *CBFB* gene to the *MYH11* gene
- t(16;16) (p13.1;q22)

Diagnostic Scheme


Peripheral Smear
CBC
Monoblasts, promonocytes and myeloblasts seen
Platelets Variable
Hb & Hct Decreased
WBC count Increased
Bone Marrow
Immunophenotype
Genetics
Cytochemistry
CD13, CD14, CD16, CD33, CD34, CD117 positive
Inversion of 16 Fusion of *CBFB* to *MYH11* gene
PAS and naphthol-ASD-chloroacetate esterase positive in abnormal eosinophils
AML inv(16)

Acute Promyelocytic Leukemia with t(15;17)(q22;q12); *PML-RARA*

Hypergranular Type

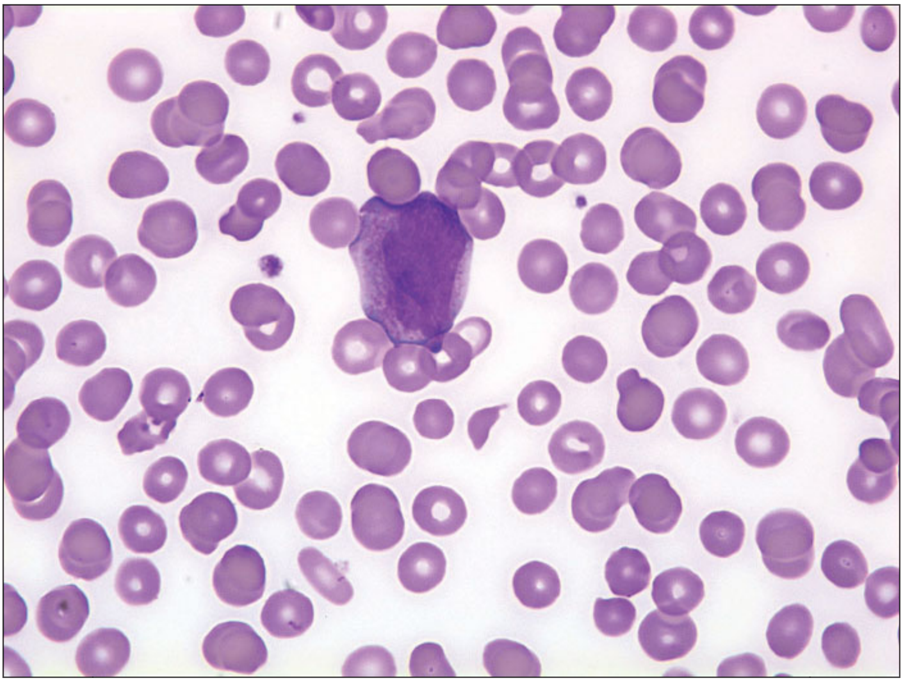


Figure IIB7-7

Peripheral blood smear.

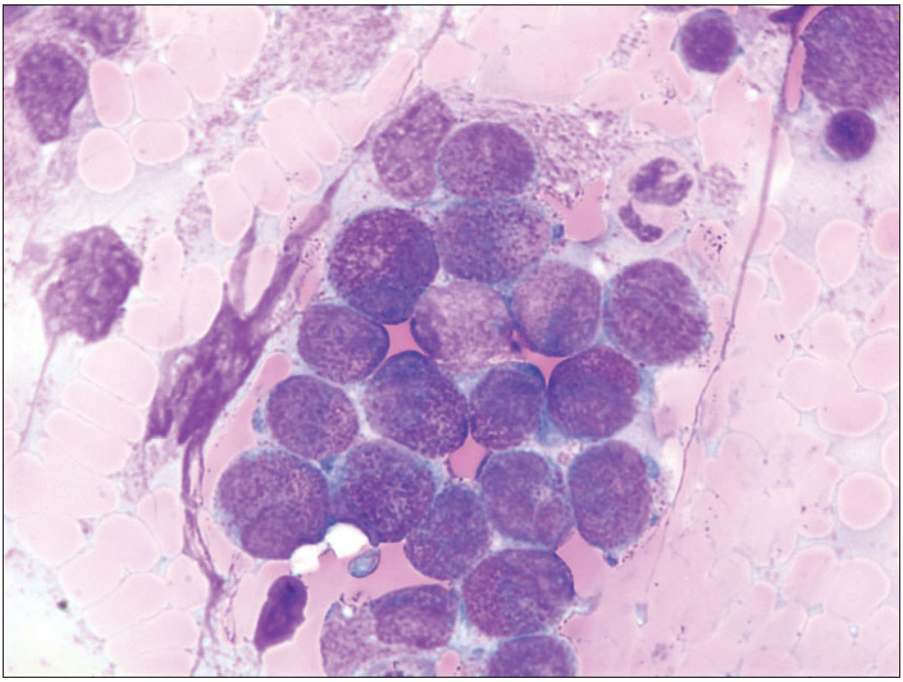


Figure IIB7-8

Bone marrow smear.

Clinical Features

- Associated with disseminated intravascular coagulation (DIC)
- Pallor, fatigue, and weakness

Pathology

- Occurs in about 5–8% of the AML cases
- Occurs at any age but most cases are young to middle aged adults
- Hypergranular (70–80% of cases) and microgranular forms exist

Laboratory Features

White Blood Cells

- Low count

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- The nucleus in the abnormal promyelocytes is irregular and often kidney-shaped or bilobed
- Large granules in the cytoplasm of the promyelocytes are dense and stain a bright pink, red, or purple
- Promyelocytes may have bundles of Auer rods randomly distributed in the cytoplasm (faggot cells)

Micrognanular Type

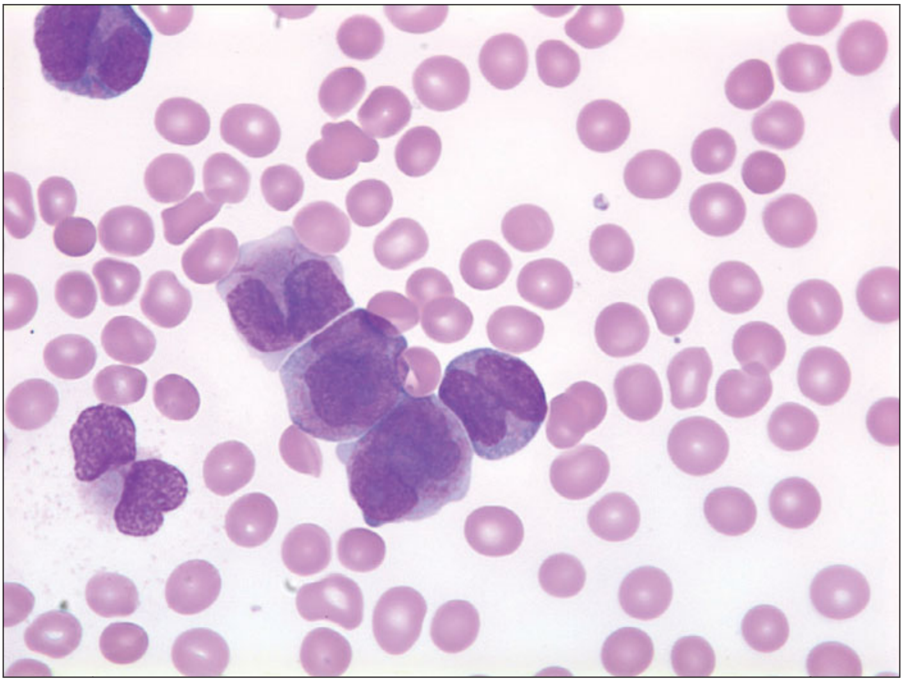


Figure IIB7-9

Peripheral blood smear.

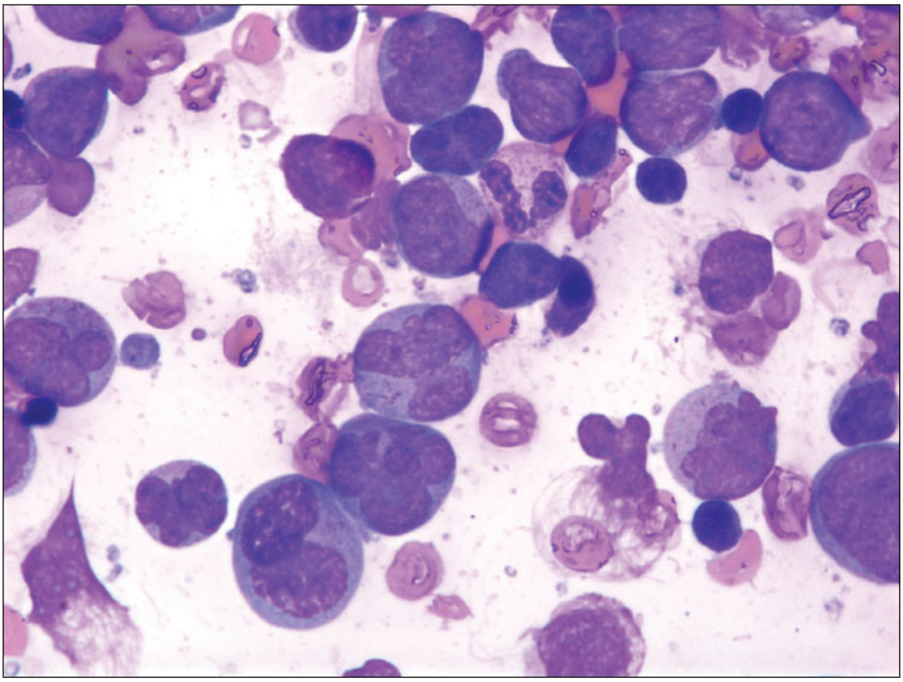


Figure **IIB7-10**

Bone marrow smear.

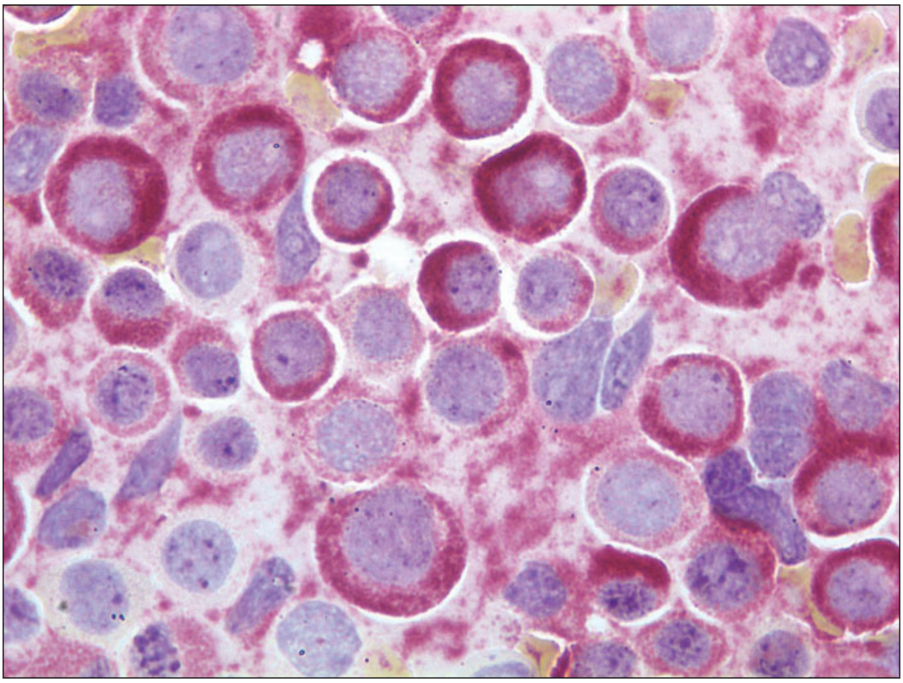


Figure **IIB7-11**

Specific esterase stain.

White Blood Cells

- Count markedly elevated with numerous abnormal microgranular promyelocytes showing reniform, irregular or bilobed nuclei

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- Predominantly bilobed and irregular nucleus in promyelocytes
- Cytoplasmic granules are present but smaller than the resolution of the microscope so appear absent or decreased in number
- Small number of promyelocytes will demonstrate clearly visible granules and bundles of Auer rods (faggot cells)

Cytochemistry

- Specific esterase is strongly positive
- Nonspecific esterase is typically negative

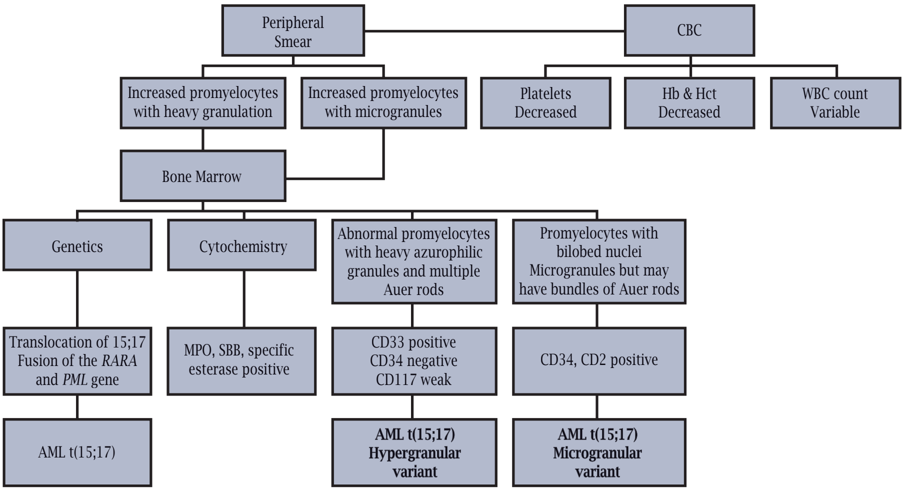
Immunophenotype

- Hypergranular type shows bright expression of CD33, typically absence of CD34, HLA-DR, and CD117 but may be weak
- CD15 and CD65 are weak or negative
- If CD56 is present, it is a worse prognosis
- In the microgranular type, there is a frequent expression of CD34 and CD2

Genetics

- t(15;17)(q22;q12)
- Translocation results in the fusion of the *RARA* gene and the *PML* gene

Diagnostic Scheme


Peripheral Smear
CBC
Increased promyelocytes with heavy granulation
Increased promyelocytes with microgranules
Platelets Decreased
Hb & Hct Decreased
WBC count Variable
Bone Marrow
Genetics
Cytochemistry
Abnormal promyelocytes with heavy azurophilic granules and multiple Auer rods
Promyelocytes with bilobed nuclei Microgranules but may have bundles of Auer rods
Translocation of 15;17 Fusion of the *RARA* and *PML* gene
MPO, SBB, specific esterase positive
CD33 positive CD34 negative CD117 weak
CD34, CD2 positive
AML t(15;17)
AML t(15;17) Hypergranular variant
AML t(15;17) Microgranular variant

AML with t(9;11)(p22;q23); *MLLT3-MLL*

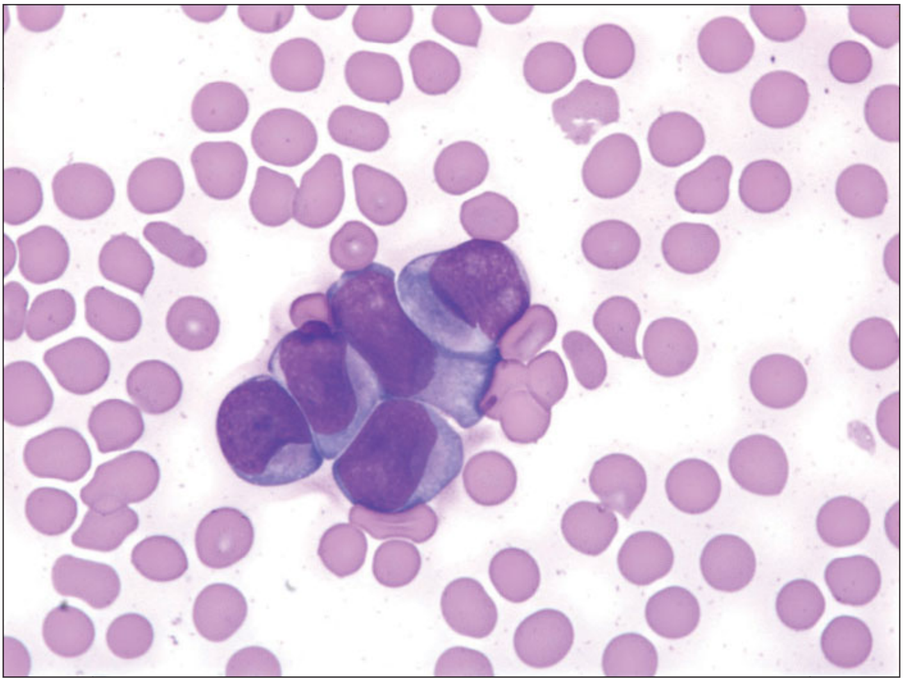


Figure **IIB7-12**

Peripheral blood smear.

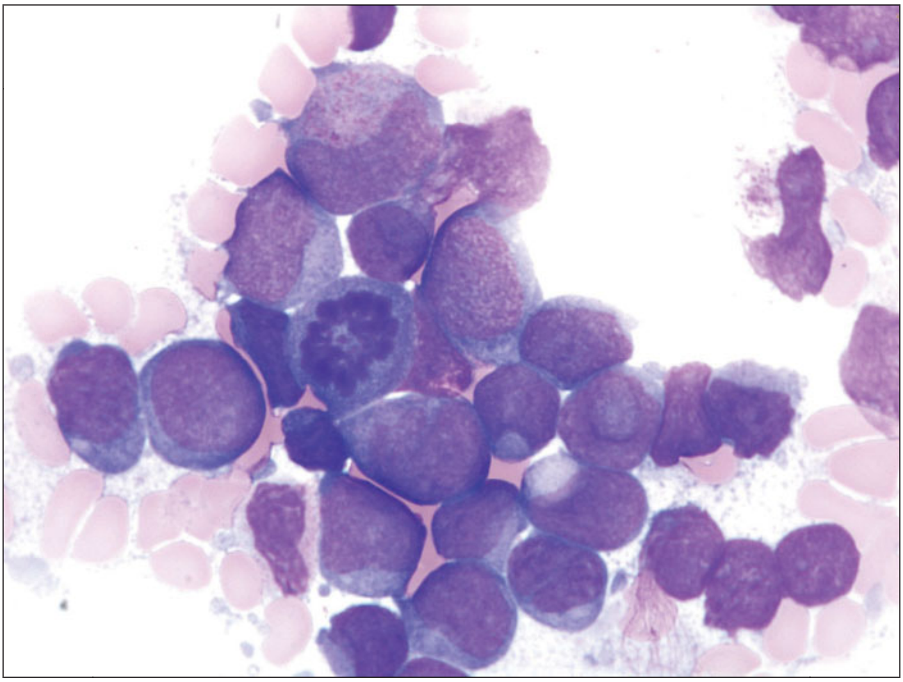


Figure **IIB7-13**

Bone marrow smear.

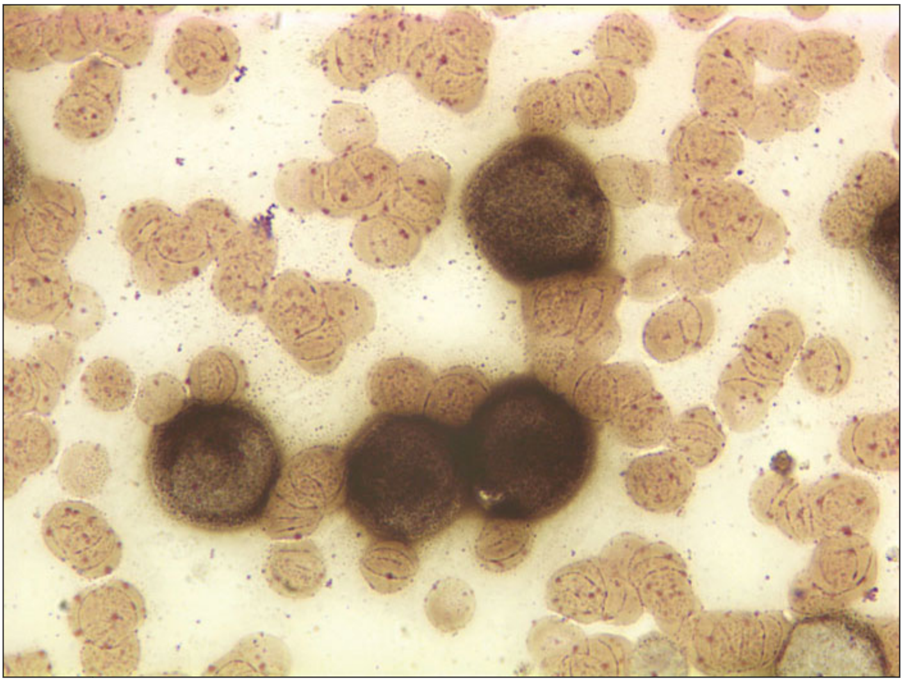


Figure IIB7-14

Nonspecific esterase stain.

Clinical Features

- Patients may present with DIC
- May have sarcomas or tissue infiltration

Pathology

- Occurs at any age but is more common in children
- Comprises about 9–12% of pediatric and 25% of adult leukemias

Laboratory Features

White Blood Cells

- Count may be low or high
- Blast morphology is variable
- Auer rods are usually absent

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- Monoblasts and promonocytes typically predominate
- Monoblasts are large and abundant intensely basophilic cytoplasm and may have pseudopod formation
- Monoblasts may have fine azurophilic granules and vacuoles
- Monoblasts usually contain round nuclei with delicate chromatin
- Promonocytes have a less basophilic cytoplasm but the nuclei are more irregular

Cytochemistry

- Nonspecific esterase reaction is strongly positive
- Monoblasts are myeloperoxidase negative

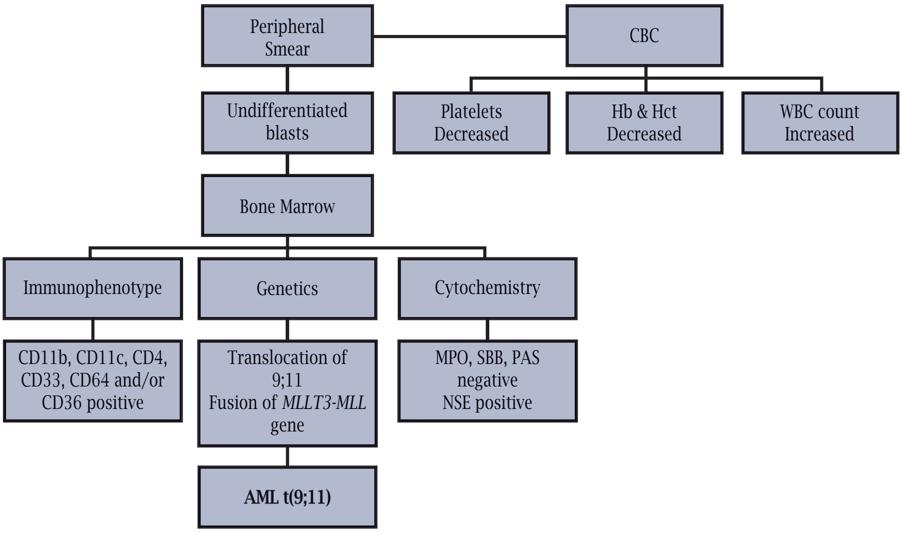
Immunophenotype

- Strong expression of CD33, CD65, CD4, and HLA-DR
- Monocytic markers, CD14, CD11b, CD11c, CD64, CD36, may be present

Genetics

- t(9;11)(p22;q23)
- Translocations cause a fusion gene of *MLLT3-MLL*

Diagnostic Scheme


Peripheral Smear
CBC
Undifferentiated blasts
Platelets Decreased
Hb & Hct Decreased
WBC count Increased
Bone Marrow
Immunophenotype
Genetics
Cytochemistry
CD11b, CD11c, CD4, CD33, CD64 and/or CD36 positive
Translocation of 9;11 Fusion of *MLLT3-MLL* gene
MPO, SBB, PAS negative NSE positive
AML t(9;11)

AML with t(6;9)(p23;q34); *DEK-NUP214*

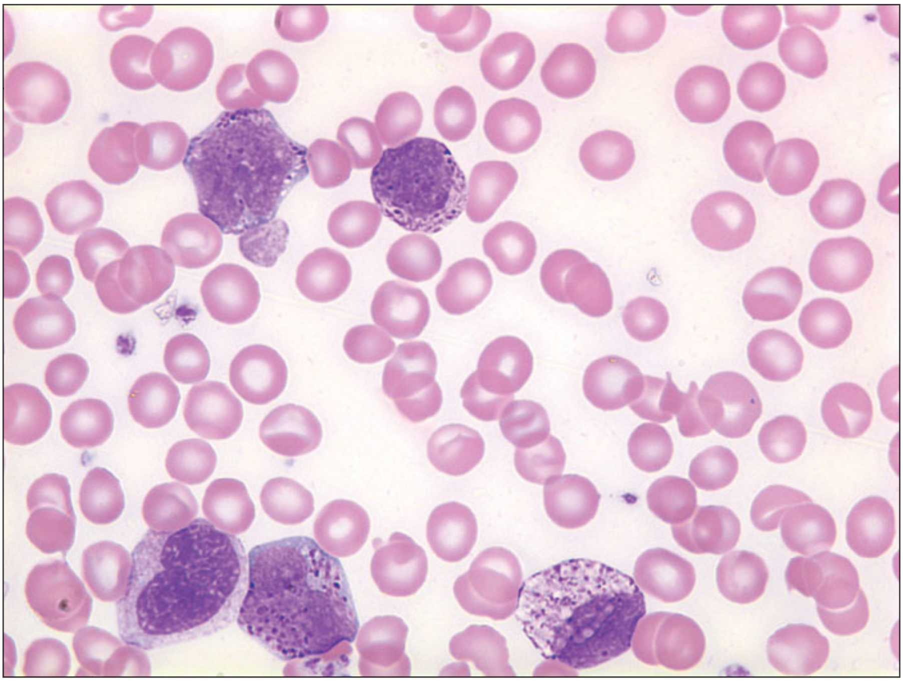


Figure IIB7-15

Peripheral blood smear.

Clinical Features

- Patients may present with a pancytopenia but usually present with anemia and thrombocytopenia

Pathology

- Occurs in both children and adults
  - Associated with any subtype of AML except promyelocytic and megakaryocytic leukemias. The most common is myelomonocytic leukemia and leukemia with maturation

Laboratory Features

White Blood Cells

- Count is usually lower than other AMLs (about 12 × 10^9/L)
- >2% basophilia
- Granulocytic dysplasia

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- Auer rods may be present
- Granulocytic and erythrocytic dysplasia
- >2% basophilia

Cytochemistry

- Myeloperoxidase reaction is strong
- Nonspecific esterase is positive if a monocytic component is present in the leukemia

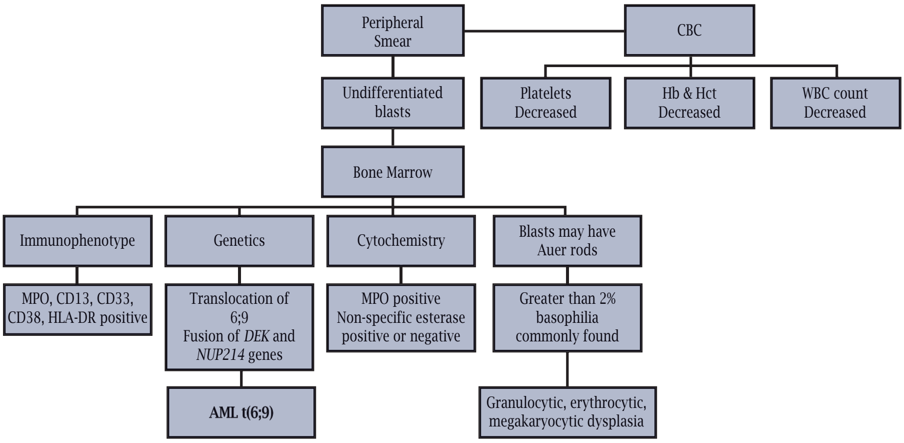
Immunophenotype

- Nonspecific myeloid with CD13, CD33, CD38, and HLA-DR
- May have the CD64 monocytic marker

Genetics

- t(6;9)(p23;q34)
- Translocation results in the fusion of *DEK* and *NUP214(CAN)*

Diagnostic Scheme


Peripheral Smear
CBC
Undifferentiated blasts
Platelets Decreased
Hb & Hct Decreased
WBC count Decreased
Bone Marrow
Immunophenotype
Genetics
Cytochemistry
Blasts may have Auer rods
MPO, CD13, CD33, CD38, HLA-DR positive
Translocation of 6;9 Fusion of DEK and NUP214 genes
MPO positive Non-specific esterase positive or negative
Greater than 2% basophilia commonly found
AML t(6;9)
Granulocytic, erythrocytic, megakaryocytic dysplasia

AML with inv(3)(q21;q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*

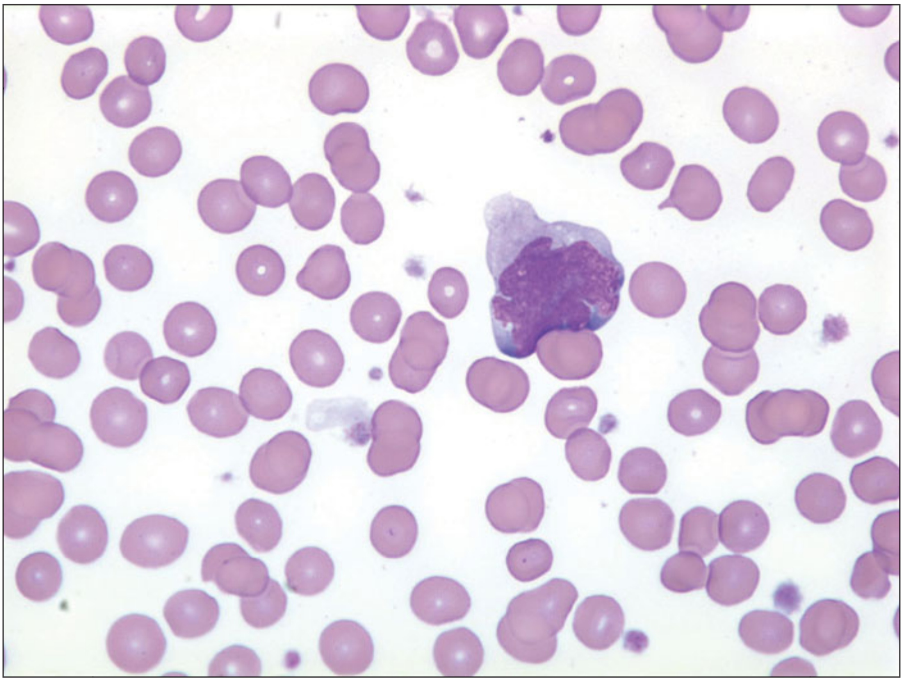


Figure **IIB7-16**

Peripheral blood smear.

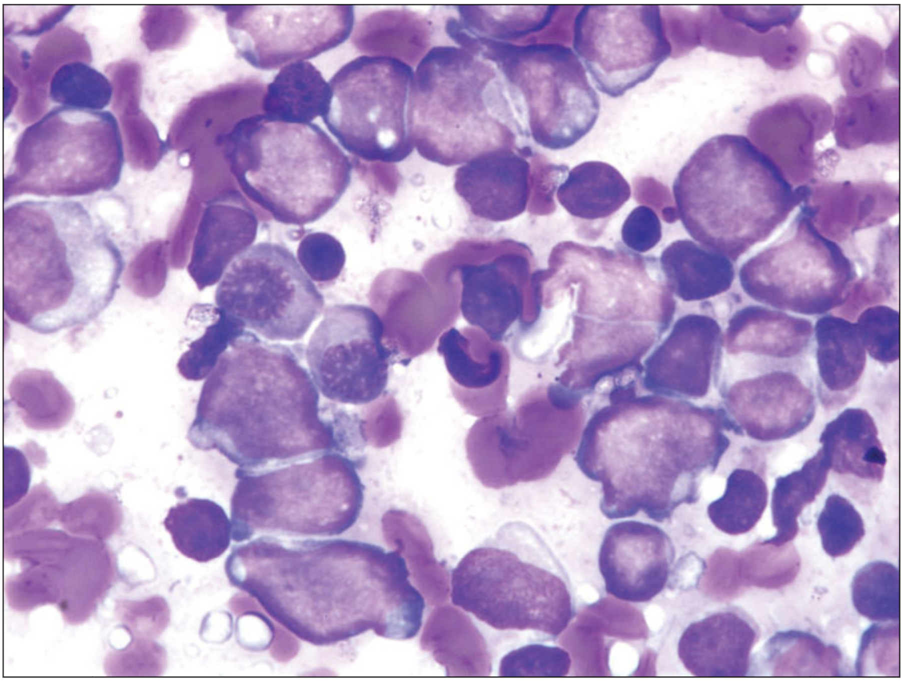


Figure **IIB7-17**

Bone marrow smear.

Clinical Features

- Most patients present with anemia and a normal platelet count
- Thrombocytopenia may be present in some patients
- Some patients have hepatosplenomegaly

Pathology

- May arise in patients with prior MDS

Laboratory Features

White Blood Cells

- Hypogranular neutrophils with pseudo-Pelger-Huët anomaly

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Count may be normal or elevated
- Giant and hypogranular

Bone Marrow

- Increased megakaryocytes but atypical or dysplastic
- Megakaryocytes may be small and mono or bilobed
- Basophils, eosinophils, and mast cells may be increased
- Multilineage dysplasia is seen

Cytochemistry

- Myeloperoxidase and Sudan black B negative
- Periodic acid-Schiff positive
- Nonspecific esterase positive (acetate)

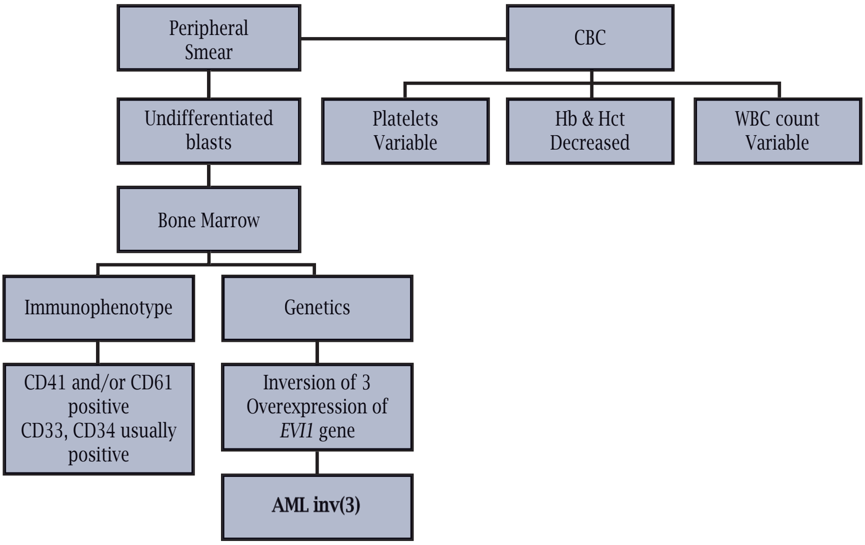
Immunophenotype

- Blasts usually express CD13, CD33, HLA-DR, CD34, and CD38
- Megakaryocytic markers of CD41 and CD61 may be expressed

Genetics

- Variety of abnormalities of the long arm of chromosome 3 but inv(3)(q21;q26.2) is the most common
- Overexpression of *EVI1,* an oncogene

Diagnostic Scheme


Peripheral Smear
CBC
Undifferentiated blasts
Platelets Variable
Hb & Hct Decreased
WBC count Variable
Bone Marrow
Immunophenotype
Genetics
CD41 and/or CD61 positive CD33, CD34 usually positive
Inversion of 3 Overexpression of *EVI1* gene
AML inv(3)

AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*

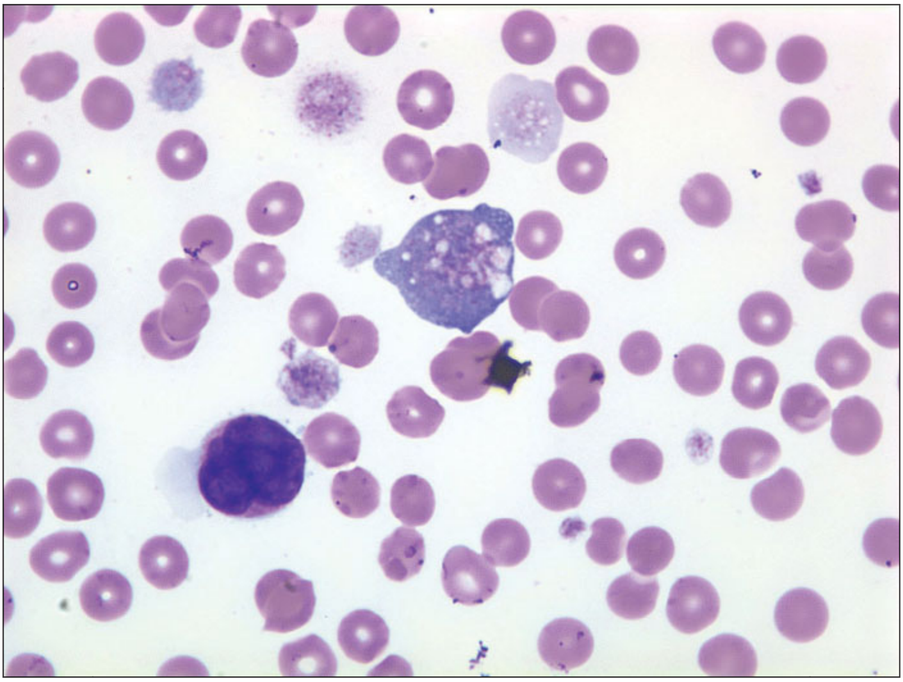


Figure **IIB7-18**

Peripheral blood smear.

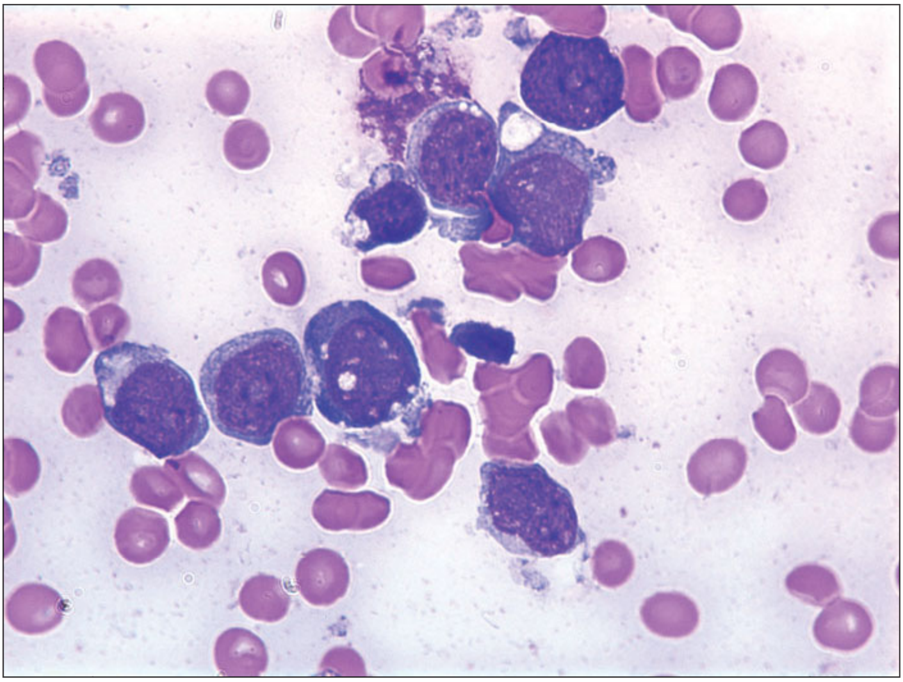


Figure **IIB7-19**

Bone marrow smear.

Clinical Features

- Cases usually restricted to infants and children <3 years of age
- Marked hepatosplenomegaly
- Often present with anemia and thrombocytopenia

Pathology

- Represents <1% of cases of AML
- Commonly in infants without Down syndrome

Laboratory Features

White Blood Cells

- Moderately elevated

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Variable
- Bizarre and atypical forms

Bone Marrow

- Small and large megakaryoblasts may be present but are usually of medium to large size
- Megakaryocytes have basophilic, agranular cytoplasm showing pseudopod formation
- Megakaryocytes nuclei are irregular or indented

Cytochemistry

- Sudan black B and myeloperoxidase reactions are negative
- Periodic acid-Schiff may be positive

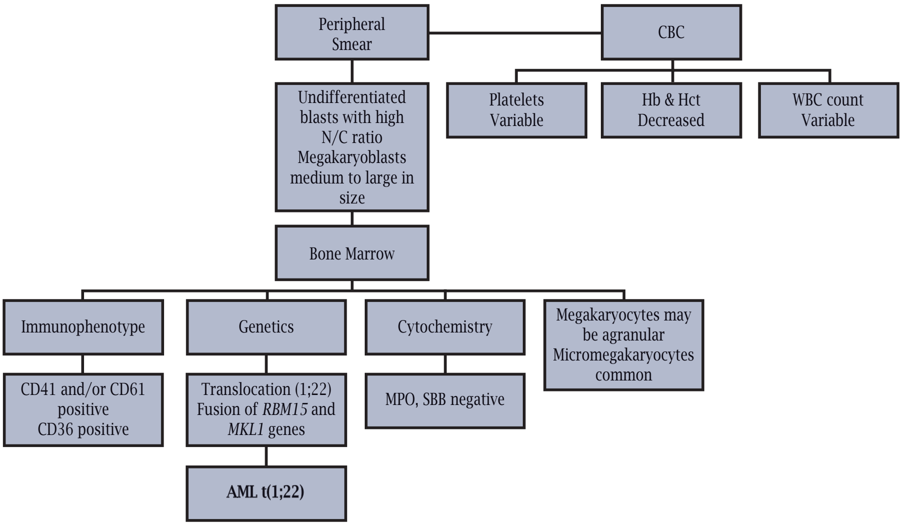
Immunophenotype

- Expression of CD41 and/or CD61

Genetics

- In most cases, t(1;22)(p13;q13) is the sole karyotypic abnormality
- A fusion gene is produced (*RBM15-MKL1*)

Diagnostic Scheme


Peripheral Smear
CBC
Undifferentiated blasts with high N/C ratio Megakaryoblasts medium to large in size
Platelets Variable
Hb & Hct Decreased
WBC count Variable
Bone Marrow
Immunophenotype
Genetics
Cytochemistry
Megakaryocytes may be agranular Micromegakaryocytes common
CD41 and/or CD61 positive CD36 positive
Translocation (1;22) Fusion of *RBM15* and *MKL1* genes
MPO, SBB negative
AML t(1;22)

Acute Myeloid Leukemia with Mutated *NPM1*

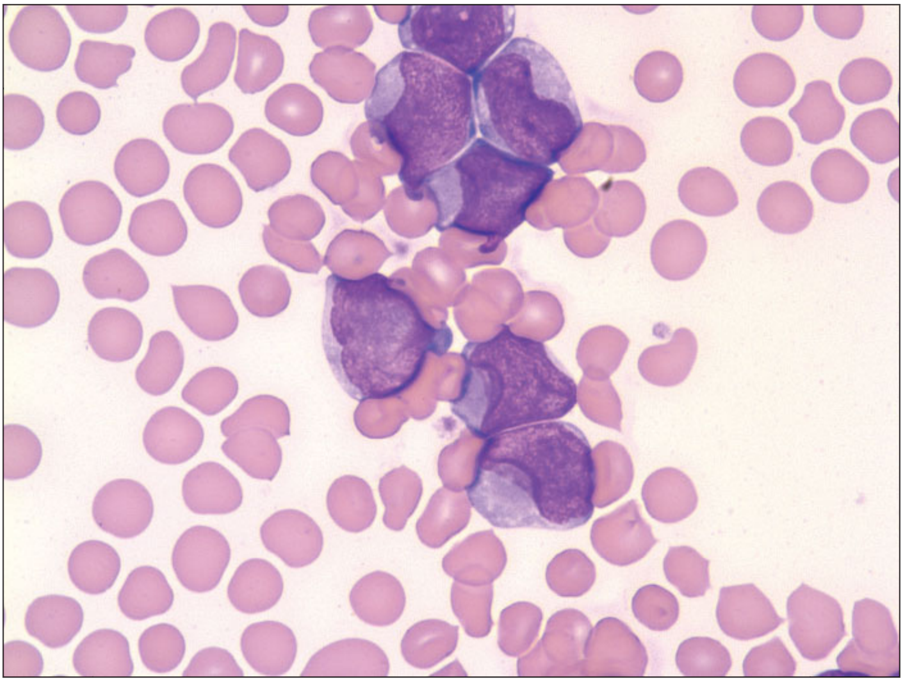


Figure IIB7-20

Peripheral blood smear.

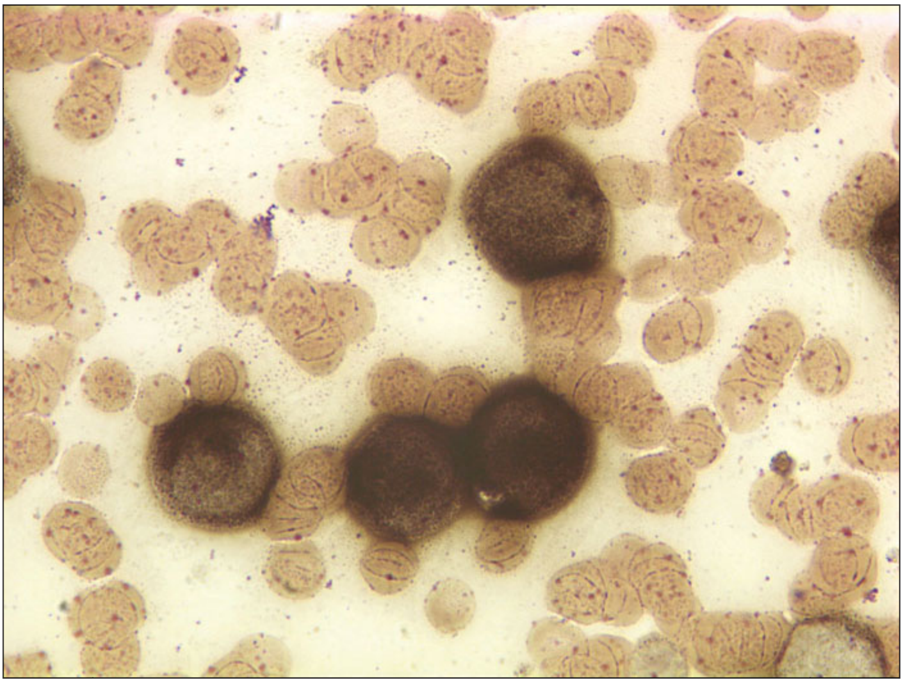


Figure IIB7-21

Nonspecific esterase stain.

Clinical Features

- Patients usually have no history of MDS or MPN
- May present with anemia and thrombocytopenia
- May have infiltration of gingiva, lymph nodes, and skin

Pathology

- Accounts for 2–8% of childhood and 27–35% of adult AML cases
- About 80–90% of acute monocytic leukemias show *NPM1* mutation

Laboratory Features

White Blood Cells

- Count is usually high

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Higher platelet count than other AMLs without *NPM1* mutation

Bone Marrow

- AML may be with or without maturation, possibly erythroid or megakaryocytic but commonly monocytic or myelomonocytic

Cytochemistry

- Specific to the cell lines involved

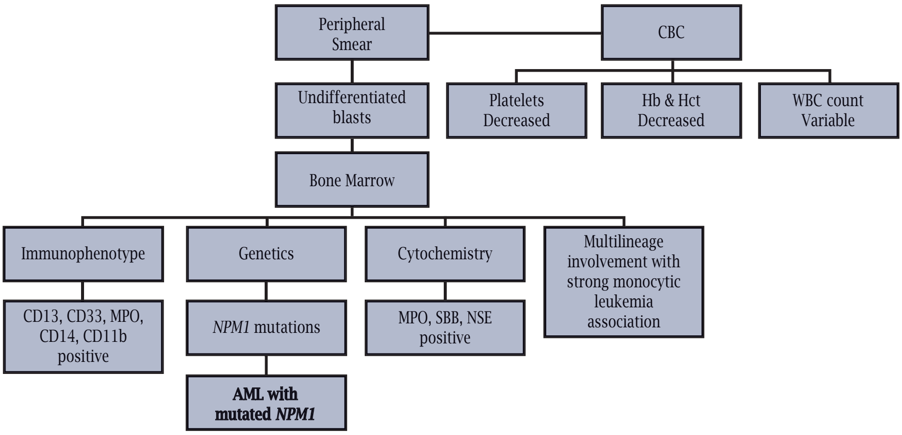
Immunophenotype

- Expression of CD13, CD33, and possibly CD14, CD11b, and CD68 (nonspecific esterase stain)

Genetics

- Mutated *NPM1*
- Usually associated with a normal karyotype

Diagnostic Scheme


Peripheral Smear
CBC
Undifferentiated blasts
Platelets Decreased
Hb & Hct Decreased
WBC count Variable
Bone Marrow
Immunophenotype
Genetics
Cytochemistry
Multilineage involvement with strong monocytic leukemia association
CD13, CD33, MPO, CD14, CD11b positive
NPM1 mutations
MPO, SBB, NSE positive
AML with mutated NPM1

Acute Myeloid Leukemia with Mutated *CEBPA*

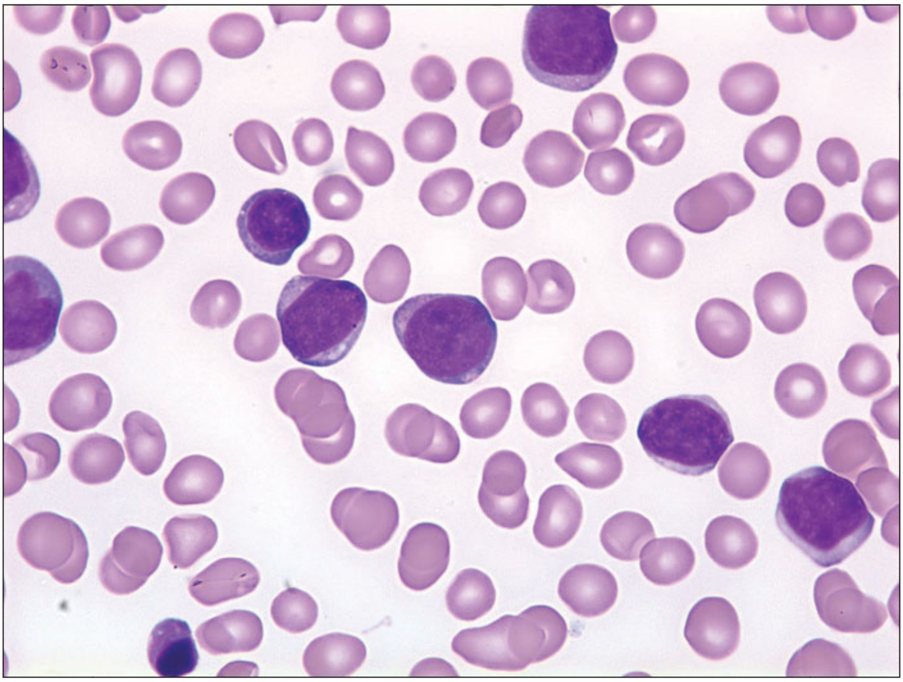


Figure IIB7-22

Peripheral blood smear.

Clinical Features

- Usually presents *de novo*

Pathology

- Occurs in about 6–15% of *de novo* AML
- Occurs in about 15–18% of AMLs with normal karyotypes

Laboratory Features

White Blood Cells

- Count is typically high

Red Blood Cells

- Normocytic/normochromic anemia but hemoglobin is higher than in most leukemias

Platelets

- Numbers decreased

Bone Marrow

- Most are associated with AML with or without maturation
- Some cases have monocytic or myelomonocytic features

Cytochemistry

- Myeloperoxidase or Sudan black B are positive if a myeloblast component is present
- Nonspecific esterase is positive when a monocytic population is present

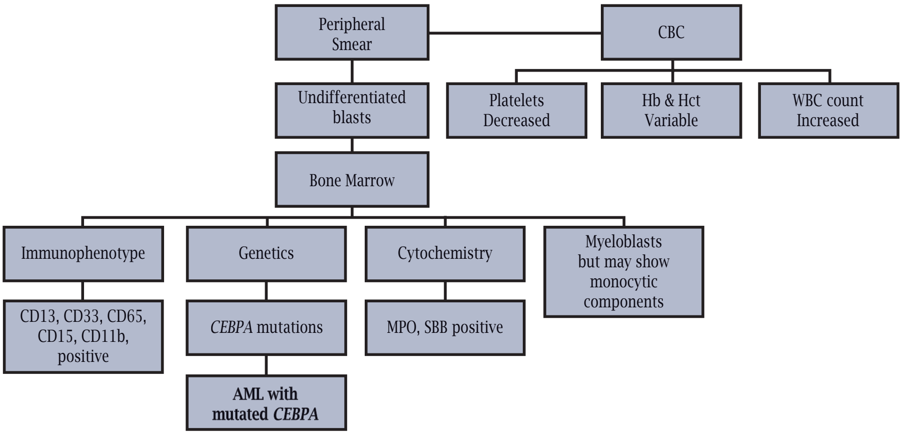
Immunophenotype

- Blasts usually express one or more of the following: CD13, CD33, CD65, CD11b and CD15
- The majority of blasts express HLA-DR and CD34

Genetics

- Mutated *CEBPA*
- Approximately 70% of the cases have a normal karyotype

Diagnostic Scheme


Peripheral Smear
CBC
Undifferentiated blasts
Platelets Decreased
Hb & Hct Variable
WBC count Increased
Bone Marrow
Immunophenotype
Genetics
Cytochemistry
Myeloblasts but may show monocytic components
CD13, CD33, CD65, CD15, CD11b, positive
CEBPA mutations
MPO, SBB positive
AML with mutated *CEBPA*

ACUTE MYELOID LEUKEMIAS, NOT OTHERWISE SPECIFIED

Acute Myeloid Leukemia with Minimal Differentiation

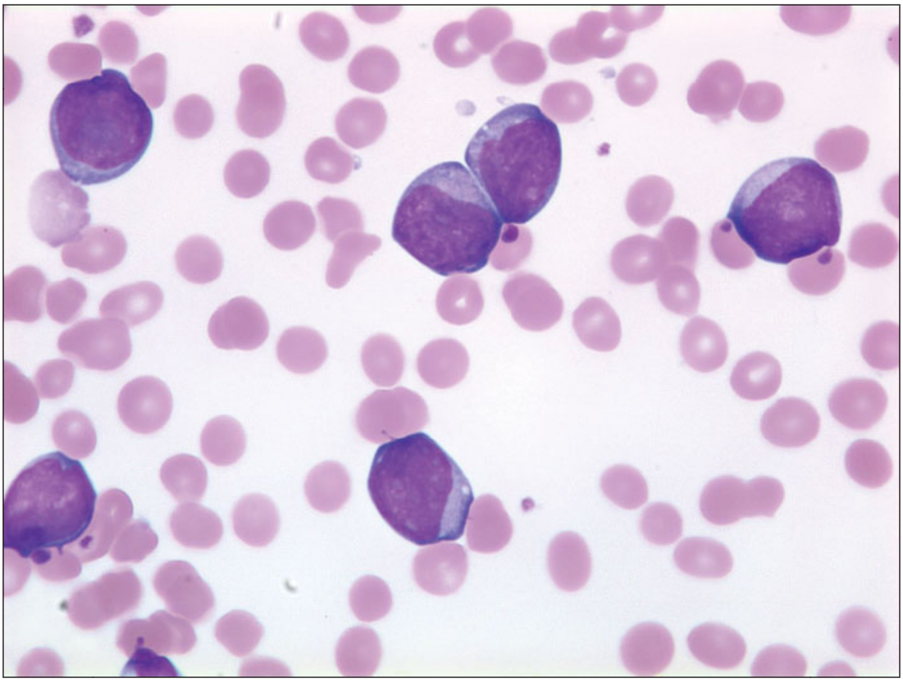


Figure IIB7-23

Peripheral blood smear.

Clinical Features

- Pallor, fatigue, and weakness from anemia
- Bleeding, bruising, and petechial hemorrhages caused by thrombocytopenia
- Infections that fail to respond to appropriate therapy

Pathology

- Make up <5% of AML
- Patients are usually infants or older adults

Laboratory Features

White Blood Cells

- Increased in 50% of patients but may be normal or decreased
- Predominant cell in peripheral blood is the myeloblast
- Auer rods are absent

Red Blood Cells

- Normocytic/normochromic anemia
- Nucleated red blood cells may be seen

Platelets

- Decreased

Bone Marrow

- Hypercellular
- Blasts are usually of medium size with dispersed nuclear chromatin
  - Round or slightly indented nuclei with one or two nucleoli
  - Cytoplasm is agranular with a varying degree of basophilia

Cytochemistry

- Myeloperoxidase, Sudan black B, and naphthol-ASD chloroacetate esterase are negative
- Alpha naphthyl acetate and butyrate esterases are negative

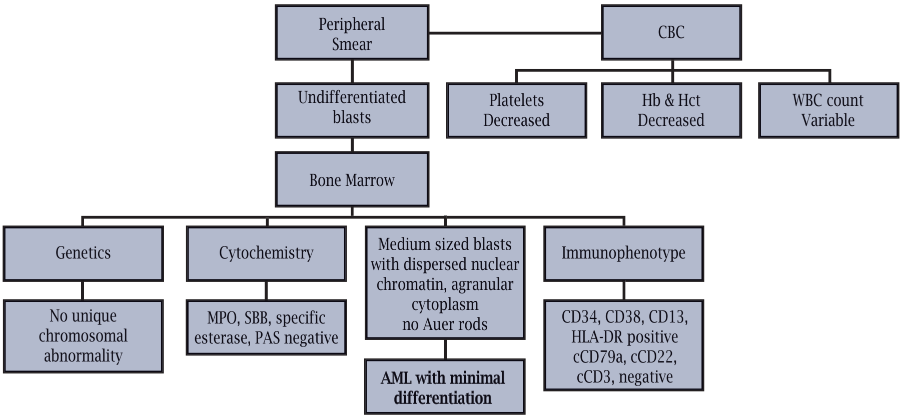
Immunophenotype

- Most cases express CD34, CD38, and HLA-DR
- CD11b, CD15, CD14, CD64, and CD65 are usually negative
- Negative for B or T cell associated antigens

Genetics

- No specific chromosomal abnormality has been identified

Diagnostic Scheme


Peripheral Smear
CBC
Undifferentiated blasts
Platelets Decreased
Hb & Hct Decreased
WBC count Variable
Bone Marrow
Genetics
Cytochemistry
Medium sized blasts with dispersed nuclear chromatin, agranular cytoplasm no Auer rods
Immunophenotype
No unique chromosomal abnormality
MPO, SBB, specific esterase, PAS negative
AML with minimal differentiation
CD34, CD38, CD13, HLA-DR positive cCD79a, cCD22, cCD3, negative

Acute Myeloid Leukemia without Maturation

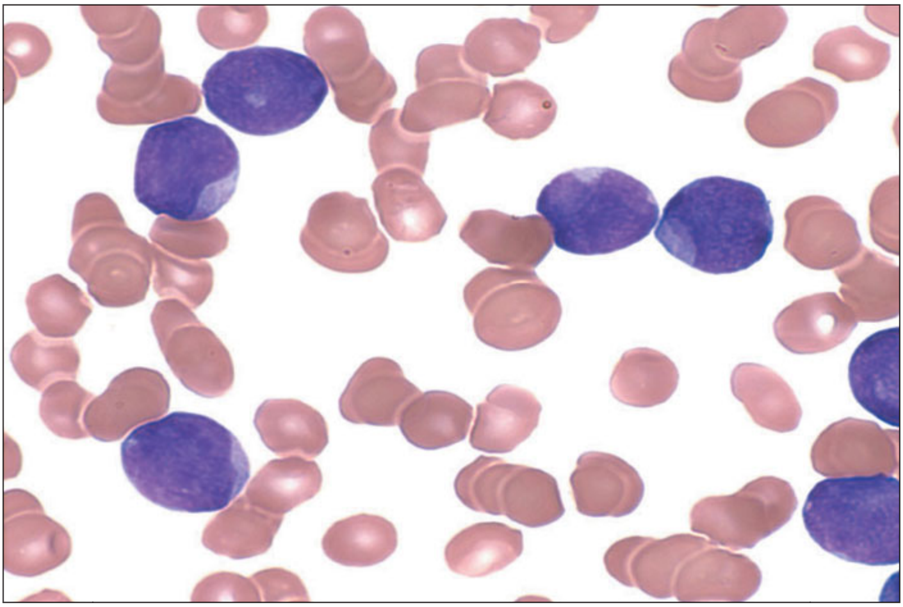


Figure IIB7-24

Peripheral blood smear.

Clinical Features

- Pallor, fatigue, and weakness from anemia
- Bleeding, bruising, and petechial hemorrhages cause by thrombocytopenia
- Infections that fail to respond to appropriate therapy

Pathology

- 5–10% of cases of AML
- Majority of patients are adults but it may occur at any age

Laboratory Features

White Blood Cells

- Usually increased but may be normal or decreased
- Predominant cell in peripheral blood is a myeloblast
- Auer rods are rare

Red Blood Cells

- Normocytic/normochromic anemia
- Nucleated red blood cells may be seen

Platelets

- Decreased

Bone Marrow

- Hypercellular
- 90% or more are myeloblasts

Cytochemistry

- Myeloperoxidase and Sudan black B are positive in a variable number of blasts but more than 3%
- Nonspecific esterases are negative

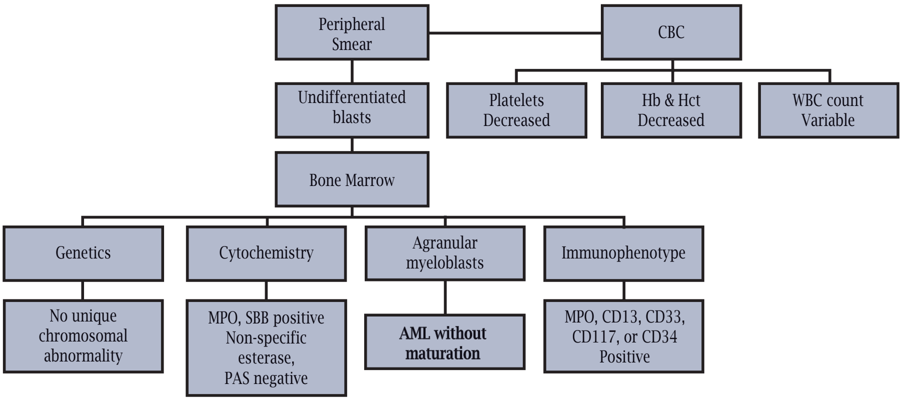
Immunophenotype

- Cells express one or more of the following: CD13, CD33, and CD117
- CD34 and HLA-DR may be positive
- CD15, CD65, CD14, CD64 are negative

Genetics

- There are no specific associated abnormalities

Diagnostic Scheme


Peripheral Smear
CBC
Undifferentiated blasts
Platelets Decreased
Hb & Hct Decreased
WBC count Variable
Bone Marrow
Genetics
Cytochemistry
Agranular myeloblasts
Immunophenotype
No unique chromosomal abnormality
MPO, SBB positive Non-specific esterase, PAS negative
AML without maturation
MPO, CD13, CD33, CD117, or CD34 Positive

Acute Myeloid Leukemia with Maturation

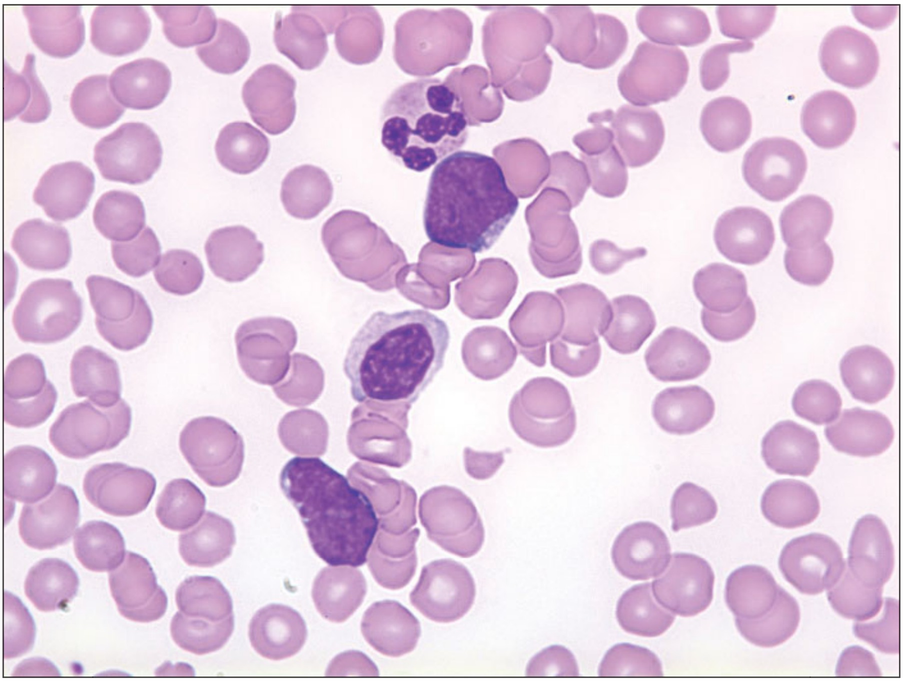


Figure IIB7-25

Peripheral blood smear.

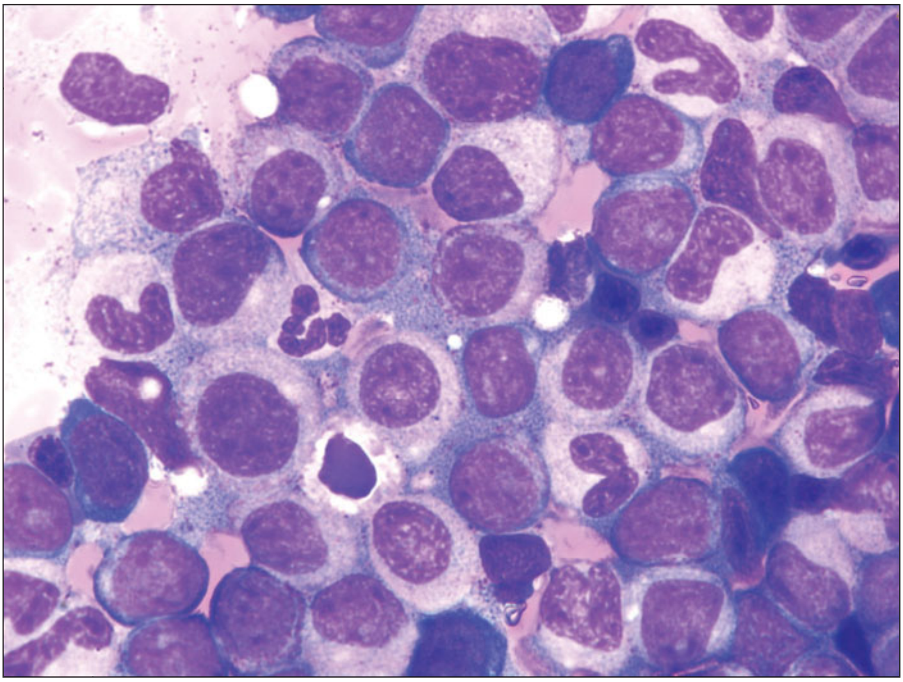


Figure IIB7-26

Bone marrow smear.

Clinical Features

- Pallor, fatigue, and weakness from anemia
- Bleeding, bruising, and petechial hemorrhages caused by thrombocytopenia
- Infections that fail to respond to appropriate therapy

Pathology

- Accounts for about 10% of cases of AML
- Occurs at any age but about 20% are <25 years of age and 40% over 60 years of age

Laboratory Features

White Blood Cells

- Count is variable
- At least 20% blasts in peripheral blood and 10% or more of the cells show granulocyte maturation
- <20% are of the monocyte lineage

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Usually decreased

Bone Marrow

- Hypercellular
- At least 20% blasts with or without azurophilic granulation
- Auer rods are common
- Maturation indicated by promyelocytes and more mature granulocytic forms present in at least 10% of nucleated cells
- Trilineage dysplasia is often present
- Eosinophil precursors may be present but do not have the cytological abnormalities
- Basophils or mast cells may be slightly increased

Cytochemistry

- Myeloperoxidase and Sudan black B positive
- Specific esterase positive

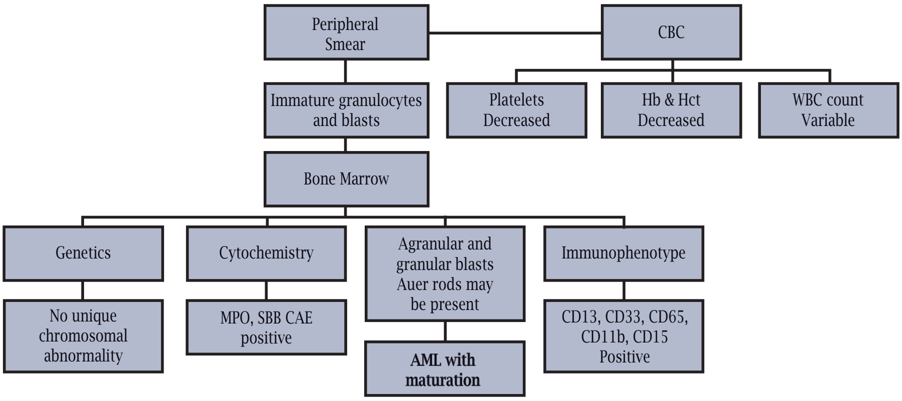
Immunophenotype

- Expression of one or more of the following: CD13, CD33, CD65, CD11b, and CD15
- CD14 and CD64 are usually absent

Genetics

- No association with recurrent genetic abnormalities

Diagnostic Scheme


Peripheral Smear
CBC
Immature granulocytes and blasts
Platelets Decreased
Hb & Hct Decreased
WBC count Variable
Bone Marrow
Genetics
Cytochemistry
Agranular and granular blasts Auer rods may be present
Immunophenotype
No unique chromosomal abnormality
MPO, SBB CAE positive
AML with maturation
CD13, CD33, CD65, CD11b, CD15 Positive

Acute Myelomonocytic Leukemia

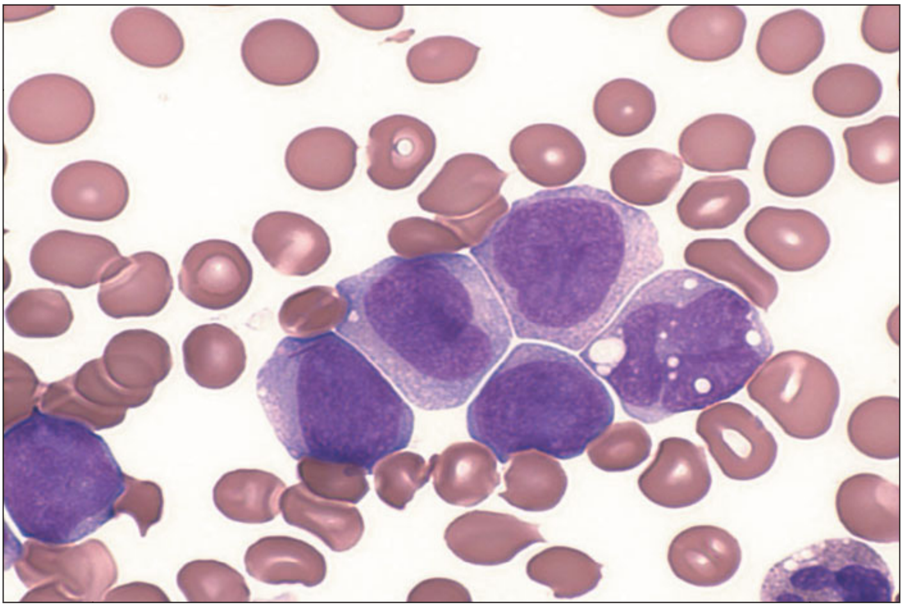


Figure IIB7-27

Peripheral blood smear.

Clinical Features

- Pallor, fatigue, and weakness from anemia
- Bleeding, bruising, and petechial hemorrhages caused by thrombocytopenia
- Infections that fail to respond to appropriate therapy
- Bone tenderness, hepatosplenomegaly, and lymphadenopathy
- Infiltration of leukemia cells in extramedullary sites
- Gingival hyperplasia is found in some cases

Pathology

- Accounts for about 5–10% of cases of AML
- Occurs in all age groups but is more common in individuals over 50 years of age
- Male to female ratio is about 1.4:1

Laboratory Features

White Blood Cells

- Count is usually increased
- Both myelocytic and monocytic differentiation occurs
- A high number of monocytic cells may be present

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased but may be normal

Bone Marrow

- At least 20% blasts (including promonocytes)
- At least 20% neutrophils and precursors
- At least 20% monocytes and precursors

Cytochemistry

- Myeloblasts are positive for myeloperoxidase, Sudan black B, and specific esterase and negative with nonspecific esterases
- Monoblasts are negative or only slightly positive for myeloperoxidase and negative or only finely granular with Sudan black B
- Nonspecific esterases are positive

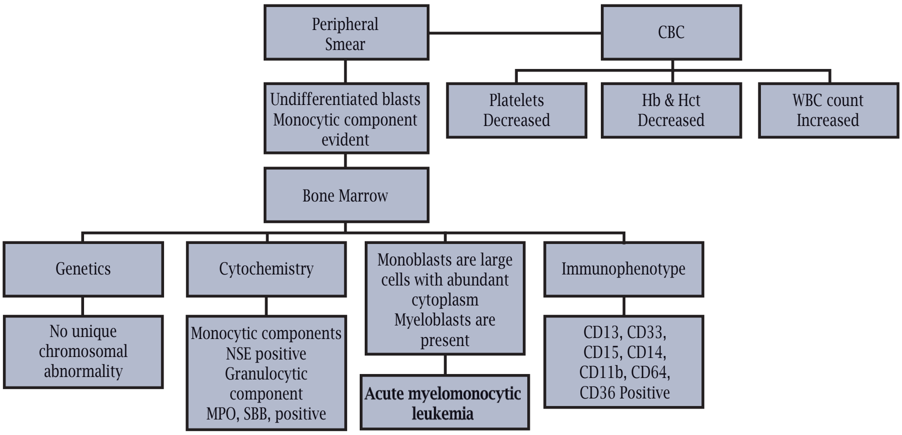
Immunophenotype

- Positive for myeloid antigen—CD13 and CD33
- Positive for monocytic markers—CD14, CD11b, CD64, and CD36

Genetics

- Nonspecific cytogenetic abnormality of +8 is present in the majority of cases

Diagnostic Scheme


Peripheral Smear
CBC
Undifferentiated blasts Monocytic component evident
Platelets Decreased
Hb & Hct Decreased
WBC count Increased
Bone Marrow
Genetics
Cytochemistry
Monoblasts are large cells with abundant cytoplasm Myeloblasts are present
Immunophenotype
No unique chromosomal abnormality
Monocytic components NSE positive Granulocytic component MPO, SBB, positive
Acute myelomonocytic leukemia
CD13, CD33, CD15, CD14, CD11b, CD64, CD36 Positive

Acute Monoblastic and Monocytic Leukemia

Monoblastic

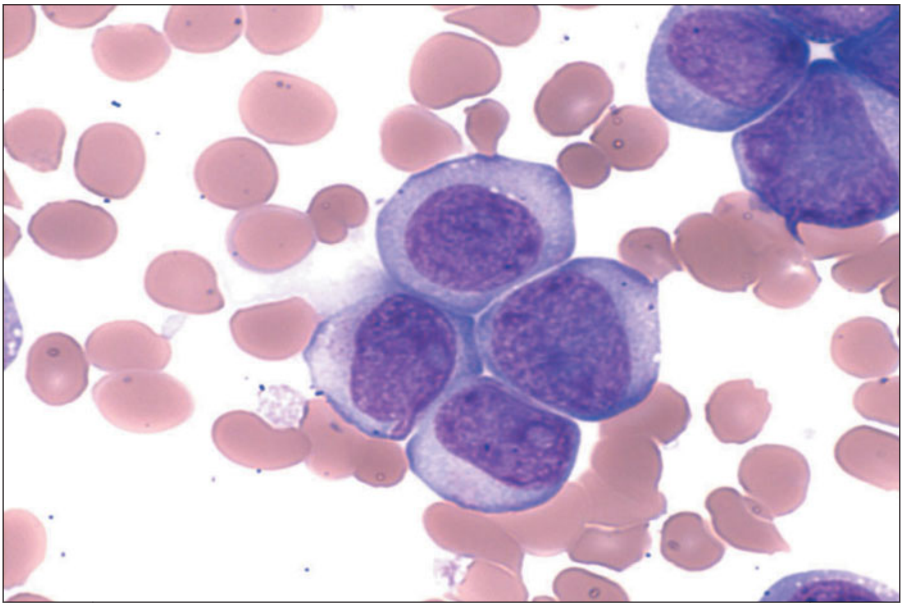


Figure **IIB7-28**

Peripheral blood smear.

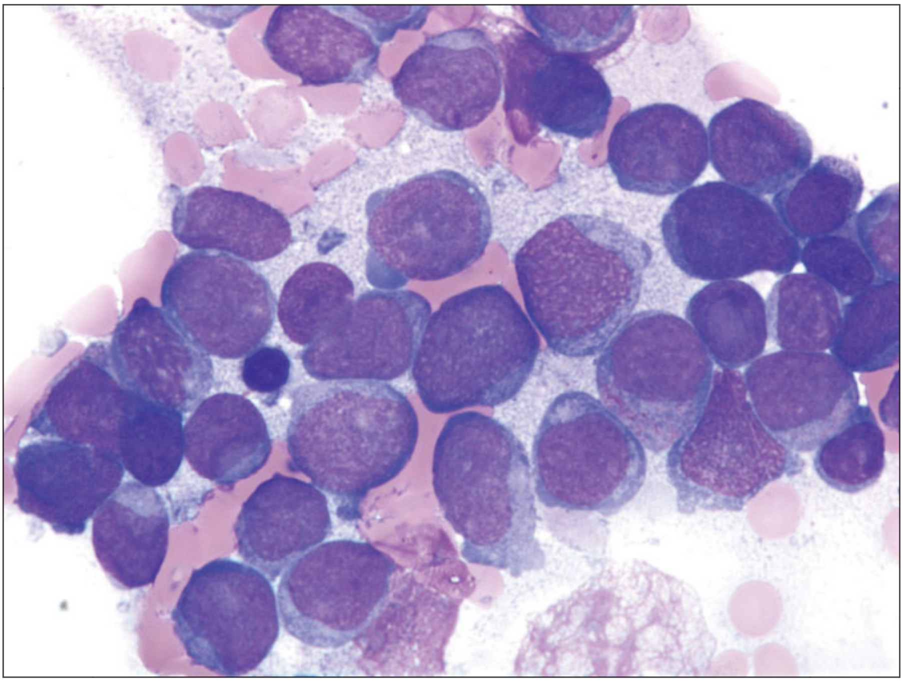


Figure **IIB7-29**

Bone marrow smear.

Monocytic

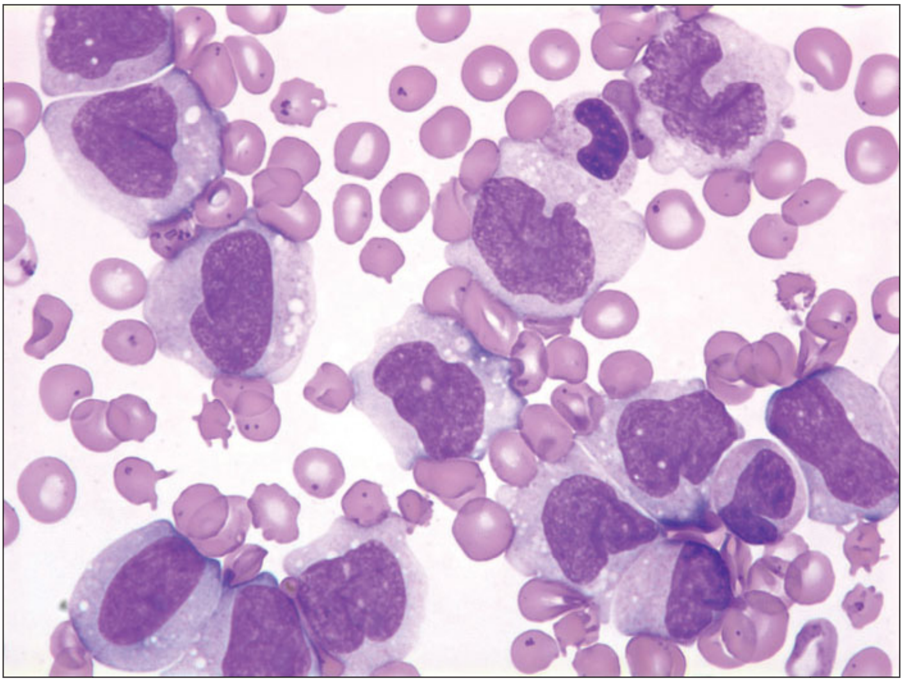


Figure **IIB7-30**

Peripheral blood smear.

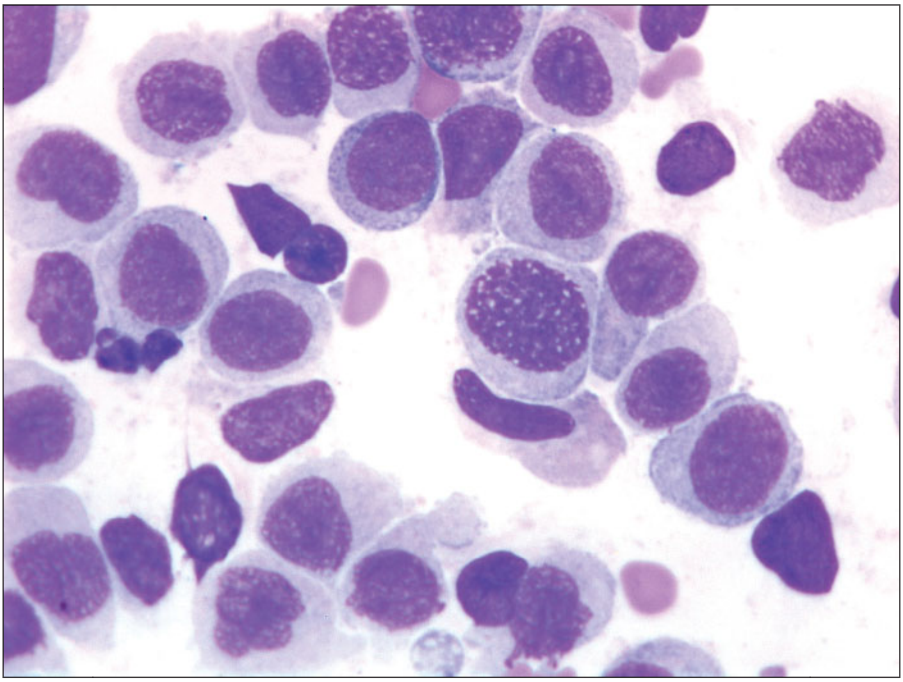


Figure **IIB7-31**

Bone marrow smear.

Clinical Features

- Bleeding disorders are the most common presentation
- Gum hyperplasia
- Splenomegaly
- Infections
- Extramedullary involvement: lymph nodes, liver, skin, spleen, central nervous system

Pathology

- Accounts for <5% of AML
- More common in young individuals

Laboratory Features

White Blood Cells

- Usually increased
- Blast morphology is variable
- Monoblasts are the predominant cells in the monoblastic type
- Promonocytes are the predominant cells in the monocytic type

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- Hypercellular
- 80% or more of the cells are of the monocytic lineage including monoblasts, promonocytes, and monocytes
- <20% are of the neutrophilic origin
- In acute monoblastic leukemia, majority of the cells are monoblasts
- In acute monocytic leukemia, majority of the cells are promonocytes

Cytochemistry

- Myeloperoxidase is typically negative or very weakly positive
- Nonspecific esterase is typically positive

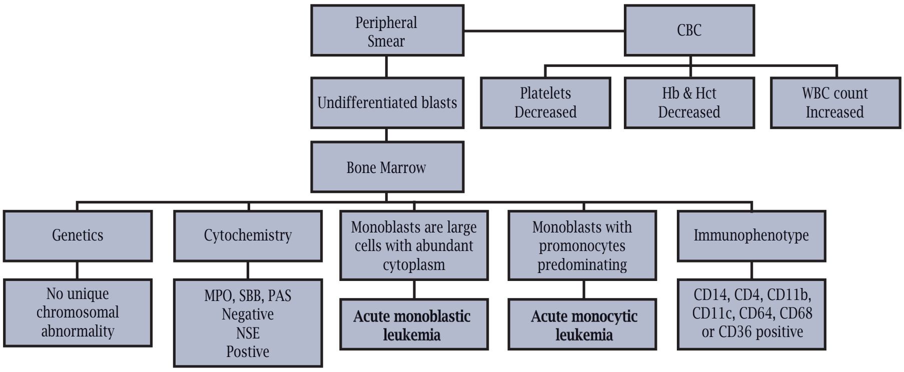
Immunophenotype

- Variable expression of CD13, CD33, CD15, and CD65
- At least two of the following markers are present: CD14, CD4, CD11b, CD11c, CD64, CD68, CD36, and lysozyme

Genetics

- Nonspecific cytogenetic abnormalities are present in most cases

Diagnostic Scheme


Peripheral Smear
CBC
Undifferentiated blasts
Platelets Decreased
Hb & Hct Decreased
WBC count Increased
Bone Marrow
Genetics
Cytochemistry
Monoblasts are large cells with abundant cytoplasm
Monoblasts with promonocytes predominating
Immunophenotype
No unique chromosomal abnormality
MPO, SBB, PAS Negative NSE Postive
Acute monoblastic leukemia
Acute monocytic leukemia
CD14, CD4, CD11b, CD11c, CD64, CD68 or CD36 positive

Acute Erythroid Leukemia

Erythroleukemia (Erythroid/Myeloid)

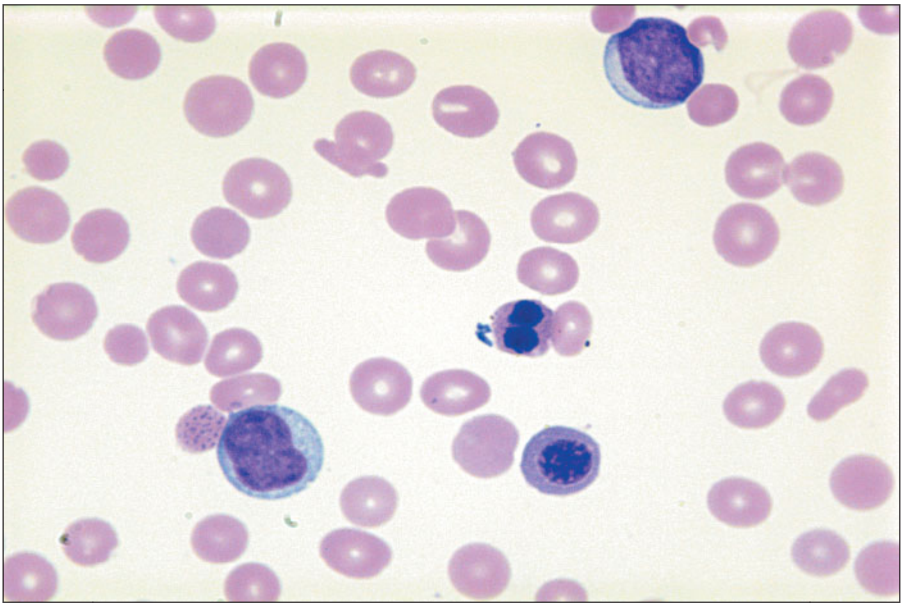


Figure **IIB7-32**

Peripheral blood smear.

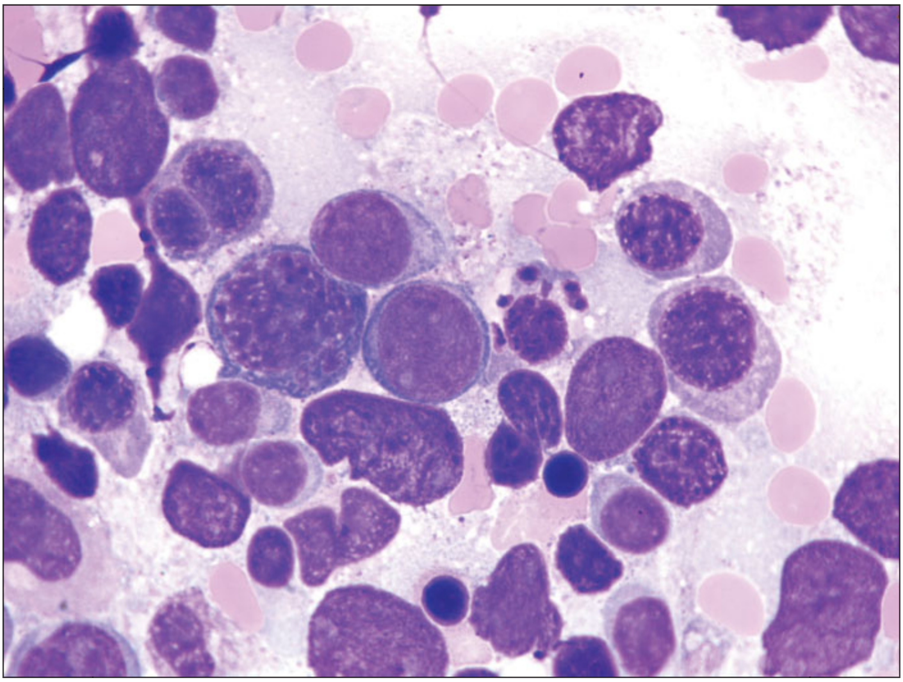


Figure **IIB7-33**

Bone marrow smear.

Clinical Features

- Weakness, fatigue, weight loss, fever
- Hepatosplenomegaly
- Petechiae, purpura

Pathology

- Two subgroups are recognized based on the number of myeloid components
- Erythroleukemia (erythroid/myeloid) accounts for <5% of the AMLs and is usually found in adults

Laboratory Features

White Blood Cells

- Variable

Red Blood Cells

- Normocytic/normochromic to macrocytic/normochromic anemia
- Anisocytosis and poikilocytosis
- Basophilic stippling
- Nucleated red blood cells

Platelets

- Variable

Bone Marrow

- Hypercellular
- All maturation stages of erythroid precursors may be present
- Dysplastic with megaloblastoid nuclei and/or bilobed or multilobed forms
- Myeloblasts are medium in size and contain a few cytoplasmic granules and occasionally Auer rods
- >50% erythroid cell and >20% myeloblasts of nonerythroid cells
- Dysgranulopoiesis and dysmegakaryopoiesis is common

Cytochemistry

- Prussian blue stain may show ring sideroblasts
- Periodic acid-Schiff stain may be positive in erythroid precursors
- Myeloperoxidase and Sudan black B are positive in the myeloblasts

Immunophenotype

- Erythroid precursors react with anti-hemoglobin A and anti-glycophorin
- The myeloid components may express one or more of the following: CD13, CD33 and CD117
- CD34 and HLA-DR may be positive

Genetics

- No specific chromosomal abnormalities are described
- Multiple structural abnormalities have been found such as –5/del(5q),–del(7q), and +8

Pure Erythroid Leukemia

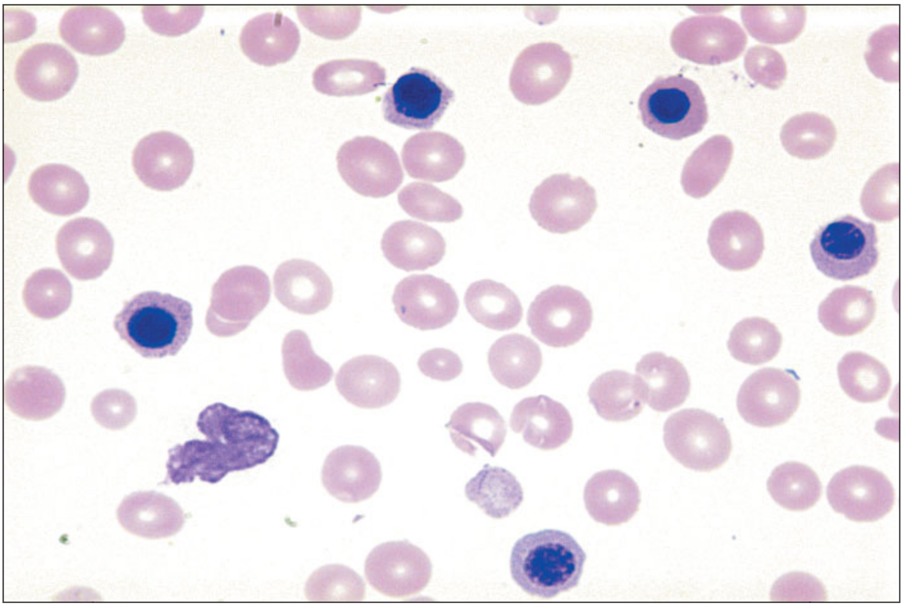


Figure **IIB7-34**

Peripheral blood smear.

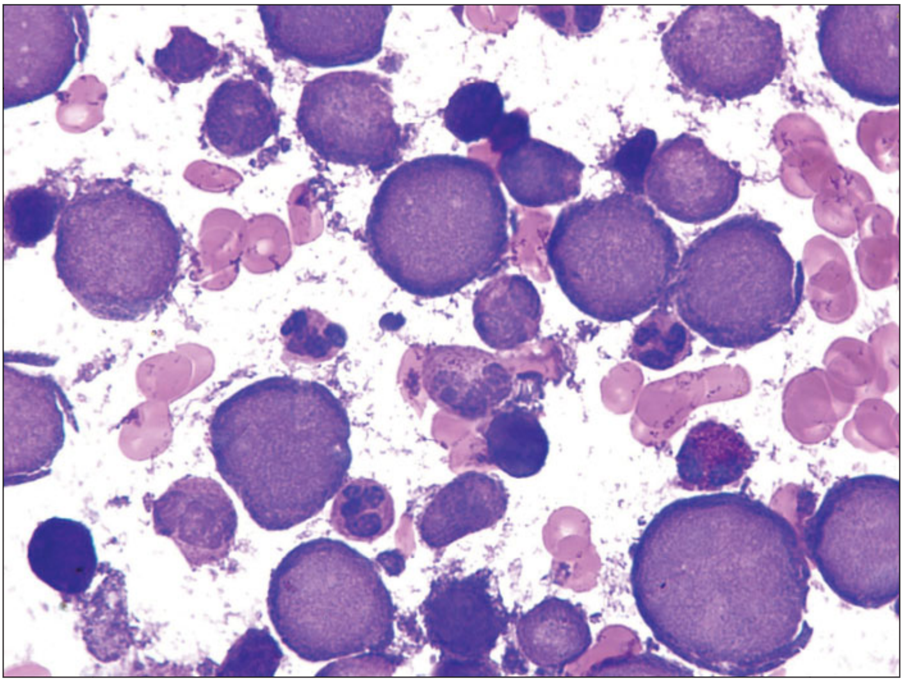


Figure **IIB7-35**

Bone marrow smear.

Clinical Features

- Weakness, fatigue, weight loss, fever
- Hepatosplenomegaly
- Petechiae, purpura

Pathology

- Pure erythroid leukemia is very rare and can occur at any age

Laboratory Features

White Blood Cells

- Count is variable

Red Blood Cells

- Normocytic/normochromic to macrocytic/normochromic anemia
- Anisocytosis and poikilocytosis
- Basophilic stippling
- Nucleated red blood cells

Platelets

- Variable

Bone Marrow

- Presence of medium to large sized erythroblasts containing round nuclei, fine chromatin and one or more nucleoli
- Cytoplasm is deeply basophilic
- >80% precursor erythroblasts

Cytochemistry

- Negative for myeloperoxidase and Sudan black B
- Periodic acid-Schiff, alpha-naphthyl acetate esterase, and acid phosphatase positive

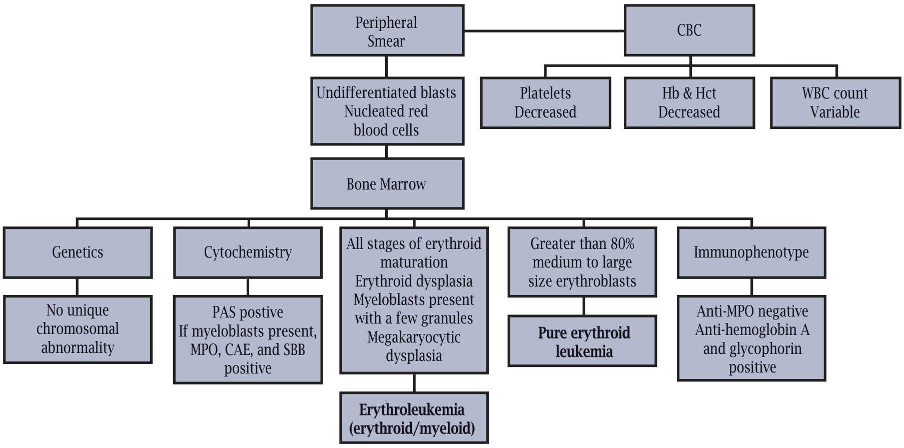
Immunophenotype

- Erythroid precursors react with anti-hemoglobin A and anti-glycophorin
- HLA-DR and CD34 are negative

Genetics

- No specific chromosomal abnormalities are described
- Multiple structural abnormalities have been found such as –5/del(5q), –7/del(7q), and +8

Diagnostic Scheme


Peripheral Smear
CBC
Undifferentiated blasts Nucleated red blood cells
Platelets Decreased
Hb & Hct Decreased
WBC count Variable
Bone Marrow
Genetics
Cytochemistry
All stages of erythroid maturation Erythroid dysplasia Myeloblasts present with a few granules Megakaryocytic dysplasia
Greater than 80% medium to large size erythroblasts
Immunophenotype
No unique chromosomal abnormality
PAS postive If myeloblasts present, MPO, CAE, and SBB positive
Pure erythroid leukemia
Anti-MPO negative Anti-hemoglobin A and glycophorin positive
Erythroleukemia (erythroid/myeloid)

Acute Megakaryoblastic Leukemia

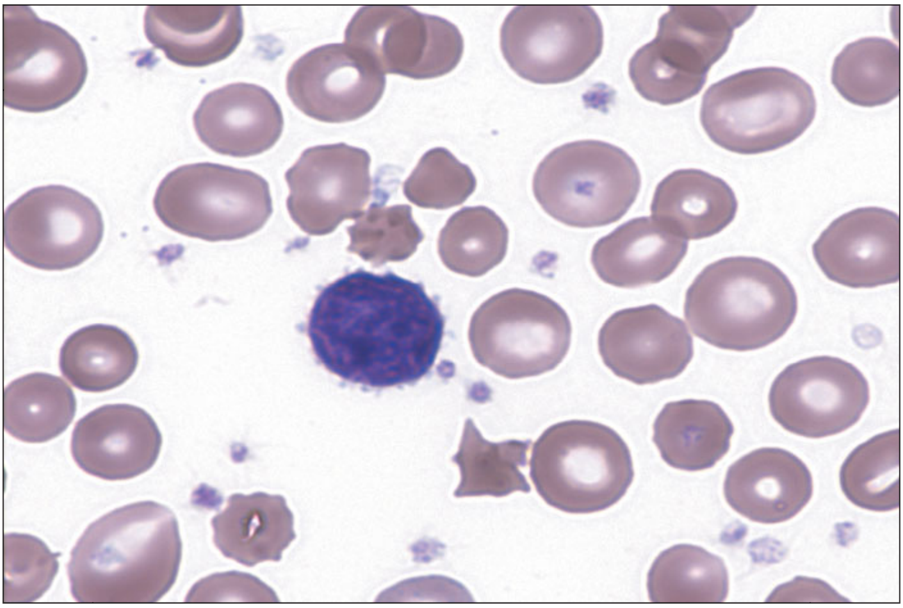


Figure IIB7-36

Peripheral blood smear.

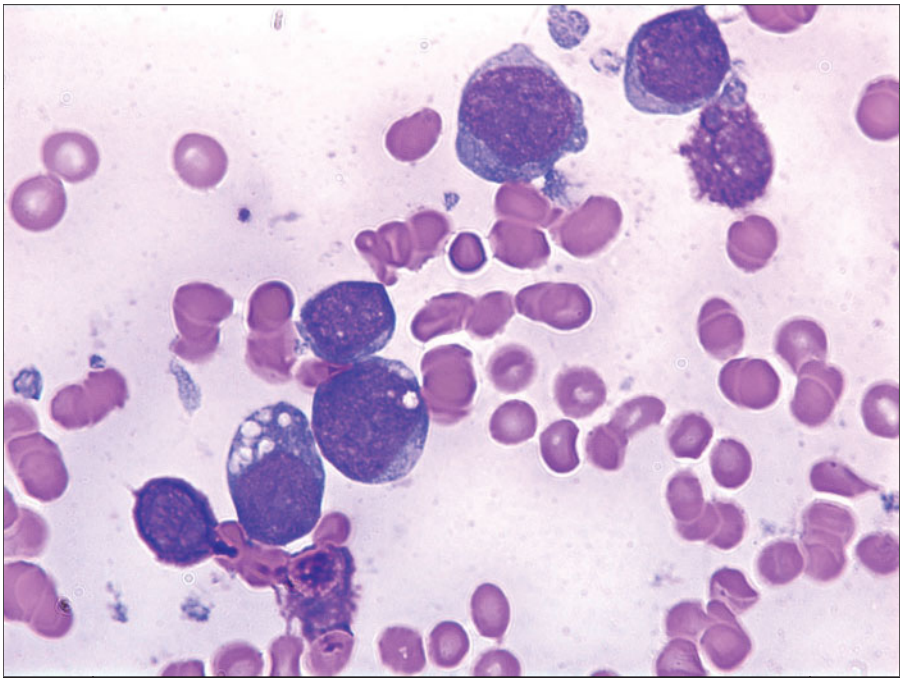


Figure IIB7-37

Bone marrow smear.

Clinical Features

- Pallor, fatigue, and weakness from anemia
- Bleeding, bruising, and petechial hemorrhages caused by thrombocytopenia
- Infections that fail to respond to appropriate therapy

Pathology

- Accounts for <5% of the AMLs
- Occurs in both adults and children

Laboratory Features

White Blood Cells

- Variable but usually decreased

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Count is variable and may be normal or increased
- Bizarre and atypical forms

Bone Marrow

- Megakaryoblasts are highly pleomorphic
- Increased reticulum fibrosis may result in a dry tap
- >20% blasts in which 50% or more are of the megakaryocytic lineage

Cytochemistry

- Myeloperoxidase and Sudan black B negative
- Periodic acid-Schiff positive
- Nonspecific esterase (acetate) positive
- Nonspecific esterase (butyrate) negative

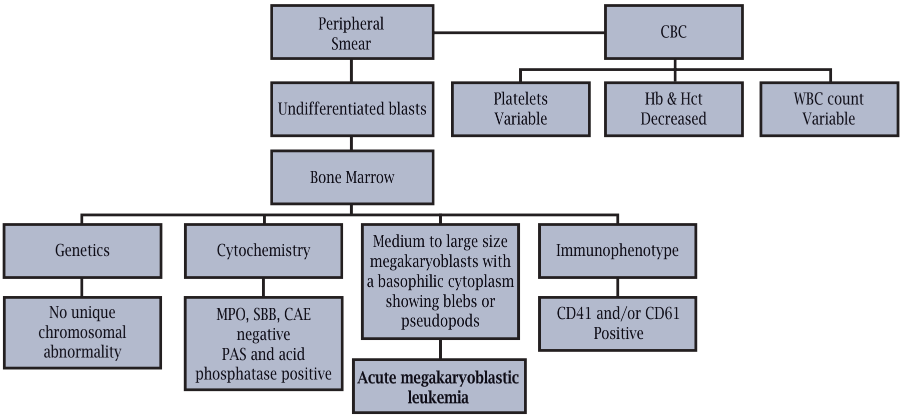
Immunophenotype

- Expression of one or more of the following: CD41 or CD61

Genetics

- No specific chromosomal abnormalities are associated

Diagnostic Scheme


Peripheral Smear
CBC
Undifferentiated blasts
Platelets Variable
Hb & Hct Decreased
WBC count Variable
Bone Marrow
Genetics
Cytochemistry
Medium to large size megakaryoblasts with a basophilic cytoplasm showing blebs or pseudopods
Immunophenotype
No unique chromosomal abnormality
MPO, SBB, CAE negative PAS and acid phosphatase positive
CD41 and/or CD61 Positive
Acute megakaryoblastic leukemia

Acute Basophilic Leukemia

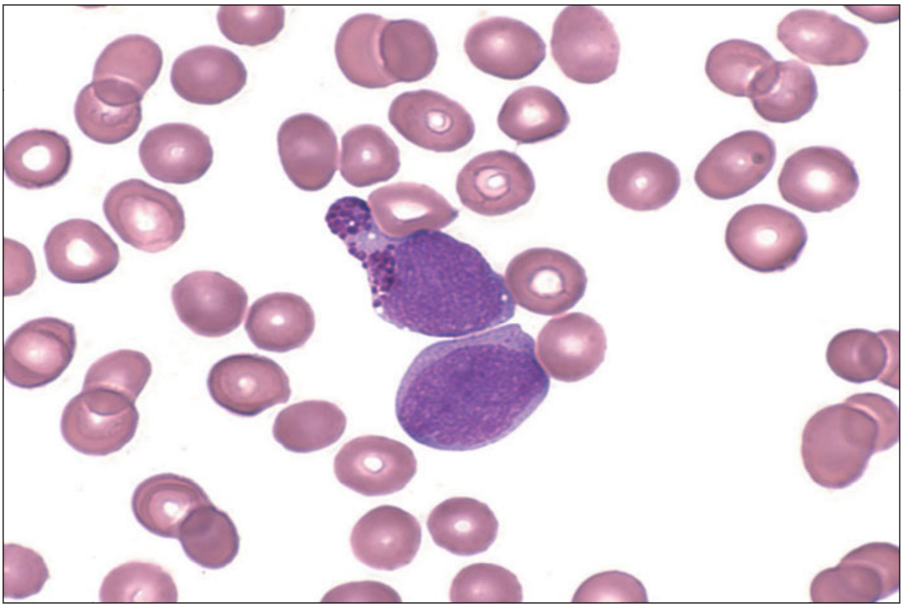


Figure **IIB7-38**

Peripheral blood smear.

Clinical Features

- Weakness, fatigue, fever, wheezing, urticaria, diarrhea, pruritus, hepatosplenomegaly

Pathology

- Very rare occurrence
- Release of basophil granules may cause shock or severe disseminated intravascular coagulation

Laboratory Features

White Blood Cells

- Normal to increased
- Increased basophils
- Abnormal basophils that resemble mast cells

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- Increased basophils with immature forms

Cytochemistry

- Myeloperoxidase and Sudan black B positive
- Toluidine blue positive

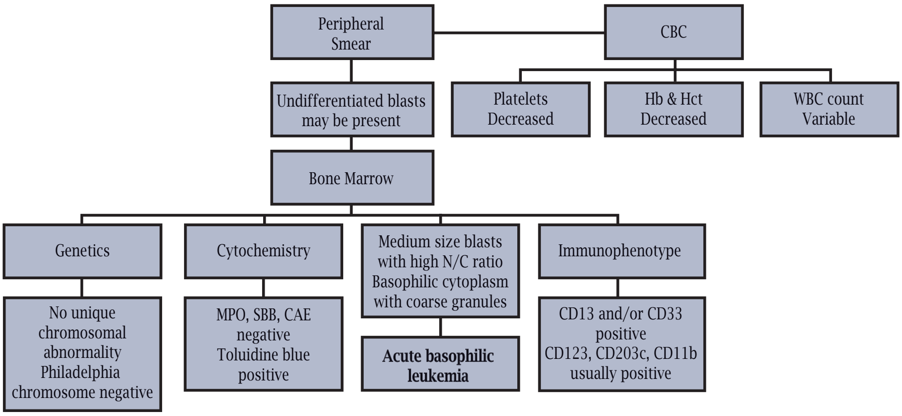
Immunophenotype

- Positive for CD13 and/or CD33
- Usually positive for CD123, CD203c, and CD11b

Genetics

- No specific chromosomal abnormalities

Diagnostic Scheme


Peripheral Smear
CBC
Undifferentiated blasts may be present
Platelets Decreased
Hb & Hct Decreased
WBC count Variable
Bone Marrow
Genetics
Cytochemistry
Medium size blasts with high N/C ratio Basophilic cytoplasm with coarse granules
Immunophenotype
No unique chromosomal abnormality Philadelphia chromosome negative
MPO, SBB, CAE negative Toluidine blue positive
Acute basophilic leukemia
CD13 and/or CD33 positive CD123, CD203c, CD11b usually positive

Acute Panmyelosis with Myelofibrosis (APMF)

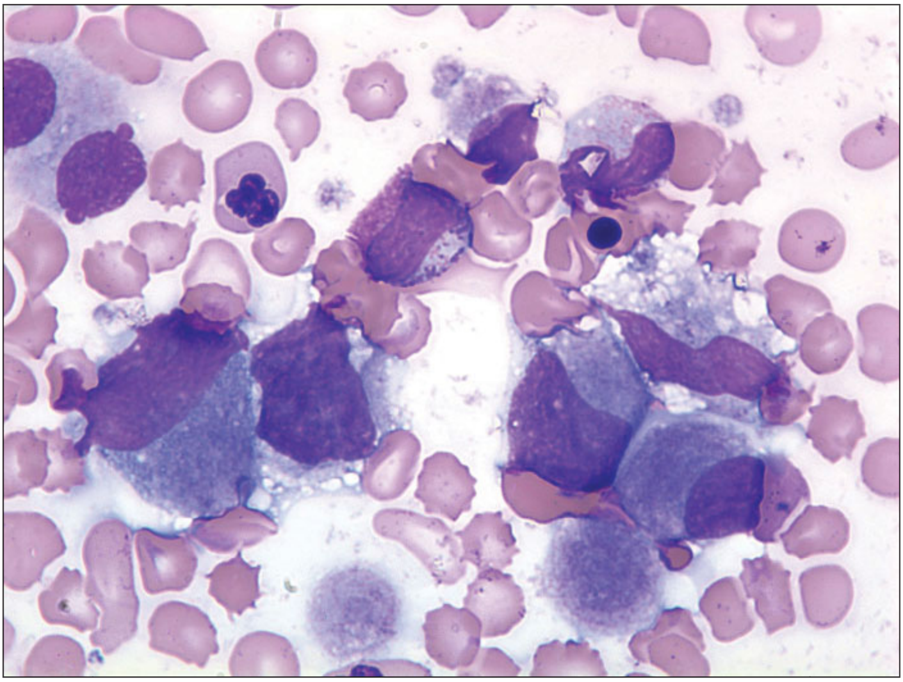


Figure **IIB7-39**

Peripheral blood smear.

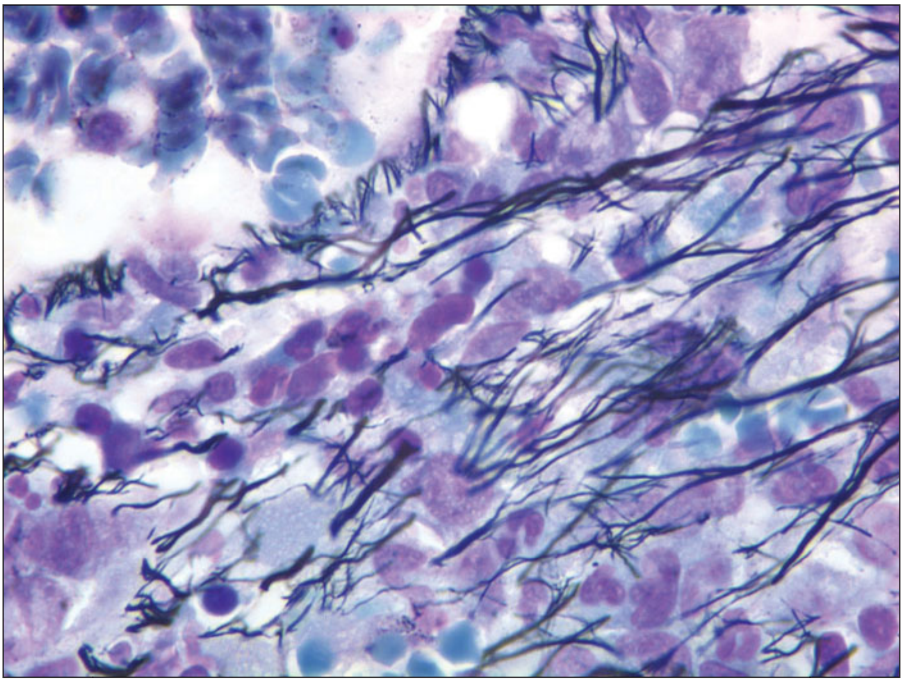


Figure **IIB7-40**

Reticulin stain.

Clinical Features

- Weakness, fatigue, fever, and bone pain
- Rapidly progressive

Pathology

- Rare form of AML
- Pancytopenia is always present

Laboratory Features

White Blood Cells

- Count is decreased

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Count is decreased
- Abnormal forms are observed

Bone Marrow

- Hypercellular
- Increased fibrotic stroma resulting in inadequate sample
- Increased erythroid, granulocyte, and megakaryocyte precursors
- Megakaryocytes are typically dysplastic

Cytochemistry

- Myeloperoxidase is negative

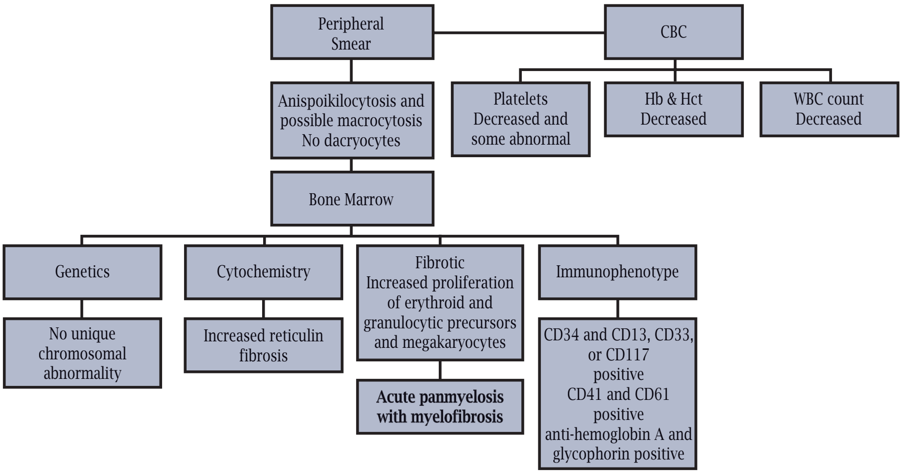
Immunophenotype

- Blasts are usually positive for CD34 and one or more of the following: CD13, CD33, and CD117

Genetics

- Usually abnormal involving chromosome 5 and/or 7

Diagnostic Scheme


Peripheral Smear
CBC
Anispoikilocytosis and possible macrocytosis No dacryocytes
Platelets Decreased and some abnormal
Hb & Hct Decreased
WBC count Decreased
Bone Marrow
Genetics
Cytochemistry
Fibrotic Increased proliferation of erythroid and granulocytic precursors and megakaryocytes
Immunophenotype
No unique chromosomal abnormality
Increased reticulin fibrosis
Acute panmyelosis with myelofibrosis
CD34 and CD13, CD33, or CD117 positive CD41 and CD61 positive anti-hemoglobin A and glycophorin positive

MYELOID PROLIFERATIONS RELATED TO DOWN SYNDROME

Myeloid Leukemia Associated with Down Syndrome

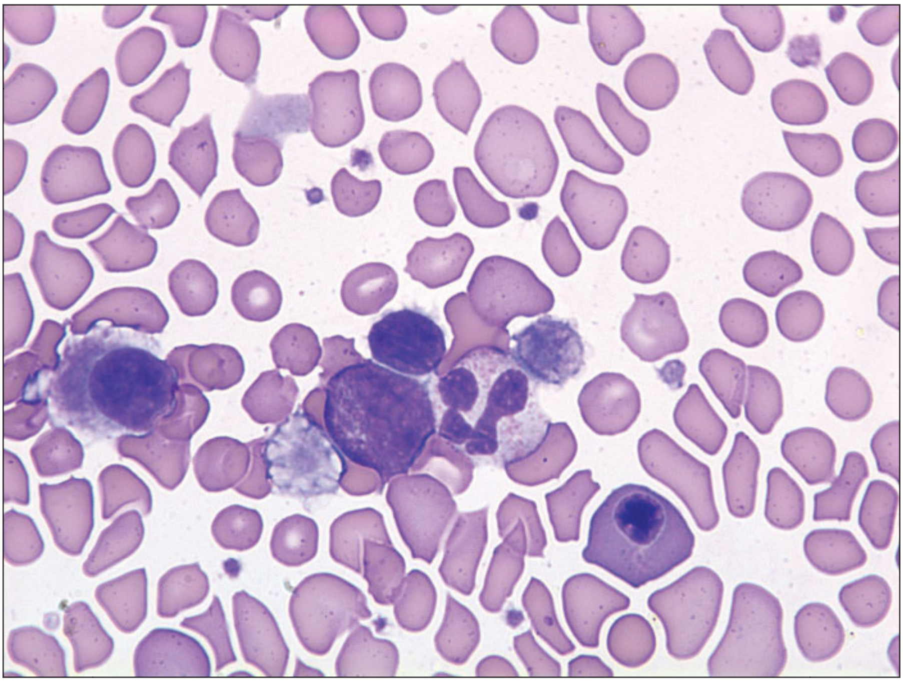


Figure IIB7-41

Peripheral blood smear.

Clinical Features

- Complications due to thrombocytopenia

Pathology

- Children with Down syndrome have a 50 times increase in the incidence of acute leukemia
- 1–2% of children with Down syndrome will develop AML and most are under 5 years of age

Laboratory Features

White Blood Cells

- Blasts may be present

Red Blood Cells

- Macrocytic anemia
- Anisopoikilocytosis
- Erythroid precursors may be seen

Platelets

- Count decreased
- Giant platelets may be seen

Bone Marrow

- Blasts have slightly irregular to round nucleus
- Cytoplasm is basophilic and blebs are usually present
- Erythroid precursors may show megaloblastic and dysplastic changes
- Dysgranulopoiesis may also be present
- Megakaryocytic series is extremely dysplastic

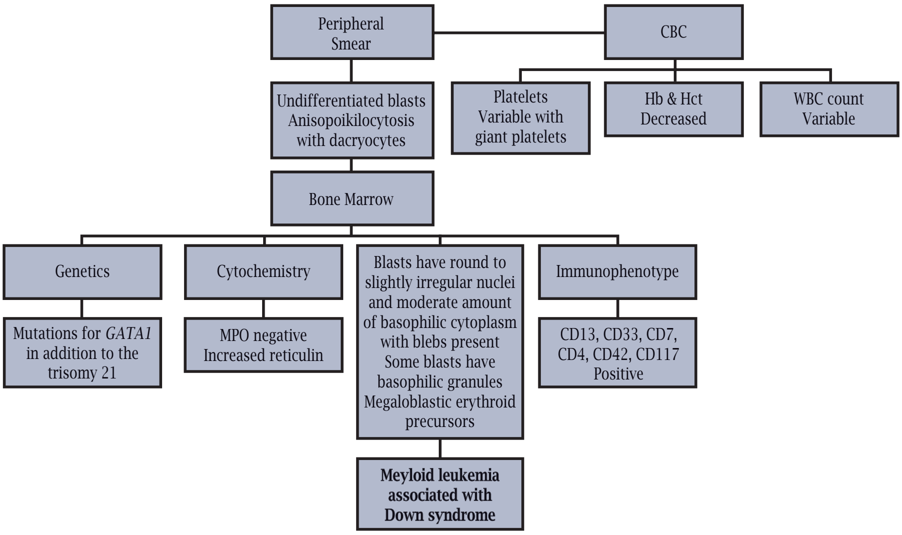
Immunophenotype

- Blasts are positive for CD117, CD13, CD33, CD7, CD4, CD42, TPO-R, IL-3R, CD36, CD41, CD61, CD71

Genetics

- Trisomy 21 and somatic mutations of the gene encoding *GATA1*

Diagnostic Scheme


Peripheral Smear
CBC
Undifferentiated blasts Anisopoikilocytosis with dacryocytes
Platelets Variable with giant platelets
Hb & Hct Decreased
WBC count Variable
Bone Marrow
Genetics
Cytochemistry
Blasts have round to slightly irregular nuclei and moderate amount of basophilic cytoplasm with blebs present Some blasts have basophilic granules Megaloblastic erythroid precursors
Immunophenotype
Mutations for GATA1 in addition to the trisomy 21
MPO negative Increased reticulin
CD13, CD33, CD7, CD4, CD42, CD117 Positive
Meyloid leukemia associated with Down syndrome

CHAPTER 8

Precursor Lymphoid Neoplasms

B LYMPHOBLASTIC LEUKEMIA/LYMPHOMA, NOT OTHERWISE SPECIFIED

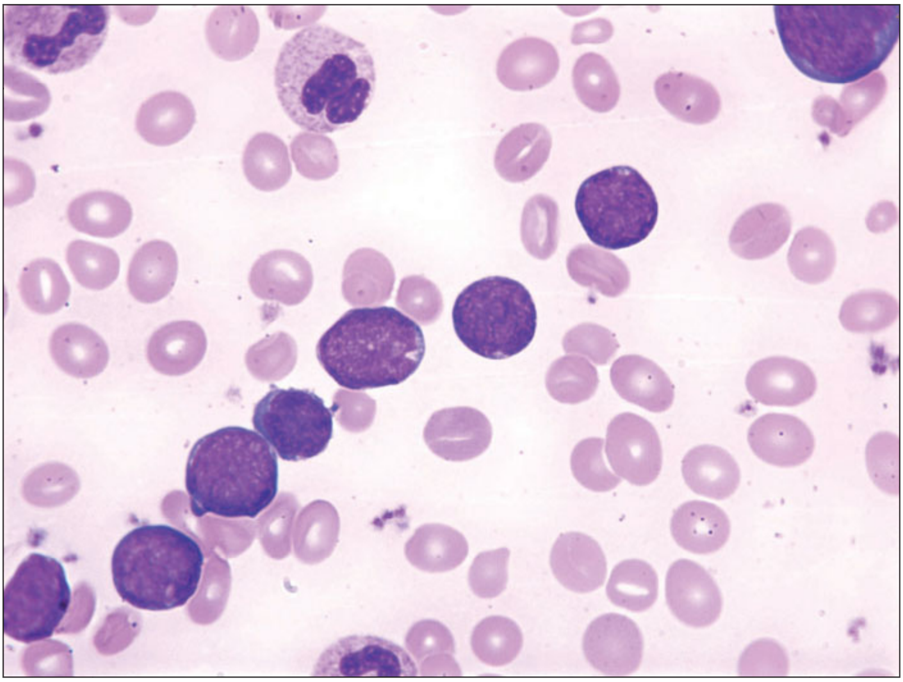


Figure IIB8-1

Peripheral blood smear.

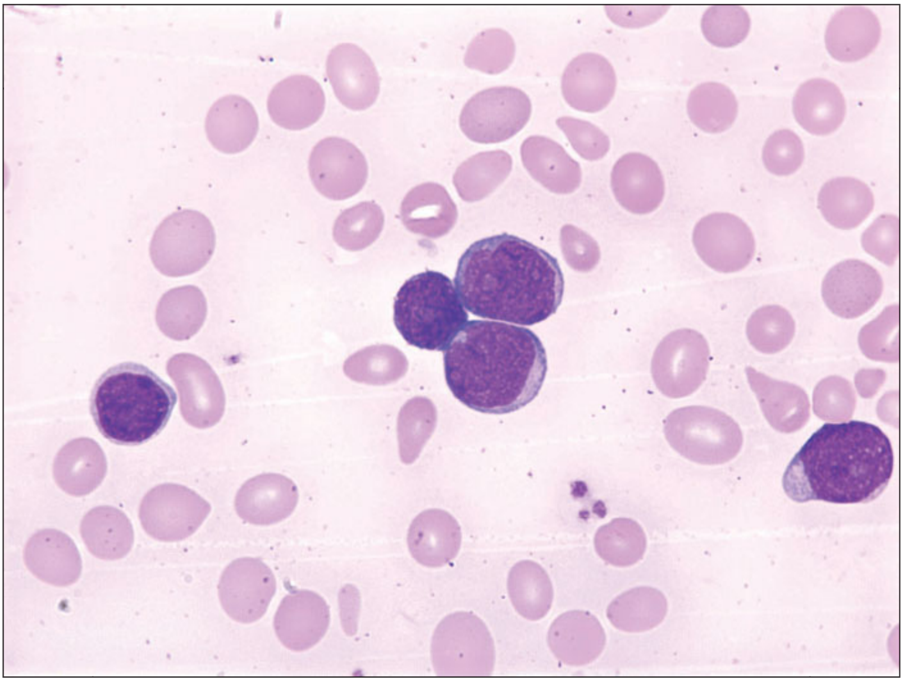


Figure IIB8-2

Peripheral blood smear.

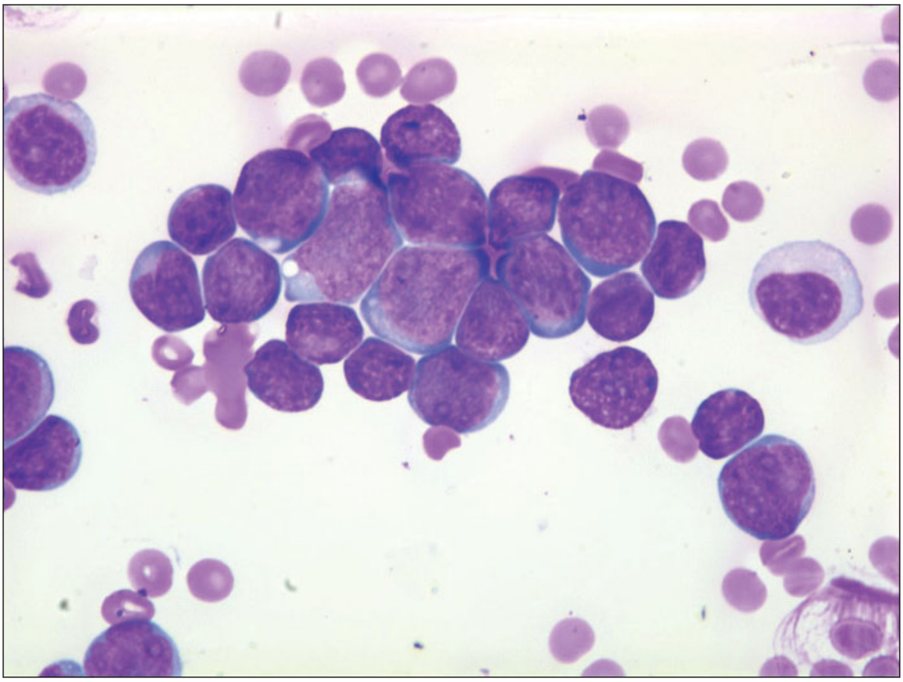


Figure IIB8-3

Bone marrow smear.

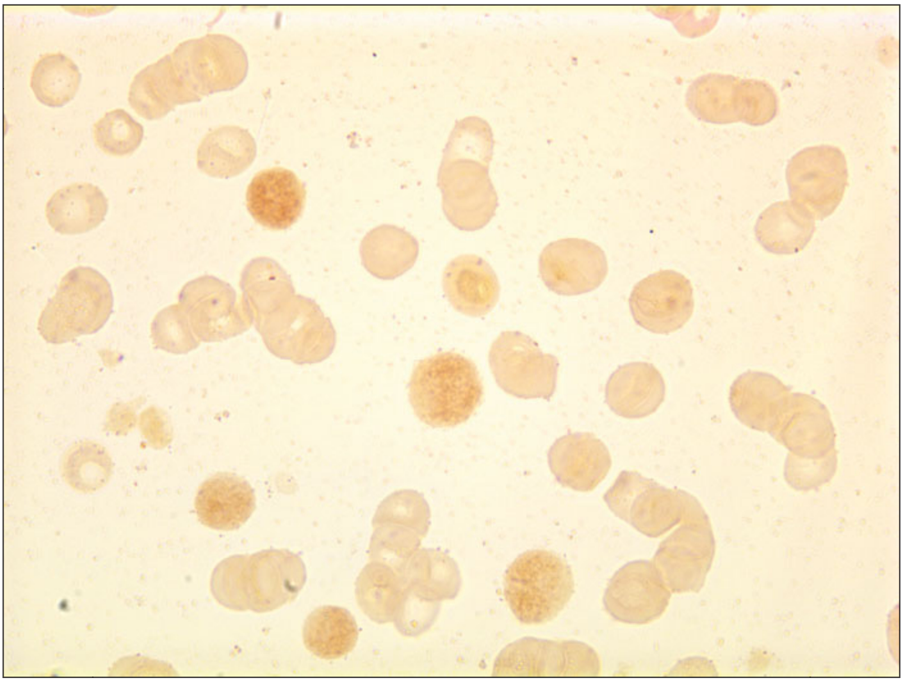


Figure IIB8-4

TdT stain.

Clinical Features

- Patients usually present with anemia, thrombocytopenia, and/or infections
- Lymphadenopathy, hepatomegaly, and splenomegaly are common
- Bone pain is a prominent feature

Pathology

- Acute lymphoblastic leukemia (ALL) is primarily a disease of children under 6 years of age but also occurs in adults
  - 80–85% are B-cell precursors (B-ALL)

Laboratory Features

White Blood Cells

- May be decreased, normal, or increased

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- Small- to medium-sized blasts with scanty cytoplasm to larger blasts with a lower N/C ratio and irregular nuclear outline
- Nuclei are moderately dispersed to condensed and nucleoli are inconspicuous

Cytochemistry

- Myeloperoxidase negative
- Periodic acid-Schiff and TdT positive

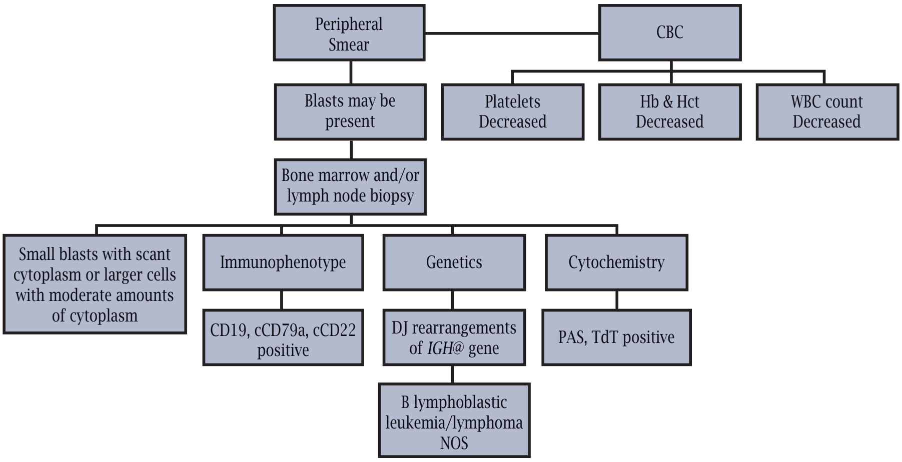
Immunophenotype

- Positive for CD19, CD79a, CD22, and nuclear TdT

Genetics

- Most cases have a DJ rearrangement of the *IGH@* gene

Diagnostic Scheme


Peripheral Smear
CBC
Blasts may be present
Platelets Decreased
Hb & Hct Decreased
WBC count Decreased
Bone marrow and/or lymph node biopsy
Small blasts with scant cytoplasm or larger cells with moderate amounts of cytoplasm
Immunophenotype
Genetics
Cytochemistry
CD19, cCD79a, cCD22 positive
DJ rearrangements of *IGH@* gene
PAS, TdT positive
B lymphoblastic leukemia/lymphoma NOS

T LYMPHOBLASTIC LEUKEMIA/LYMPHOMA

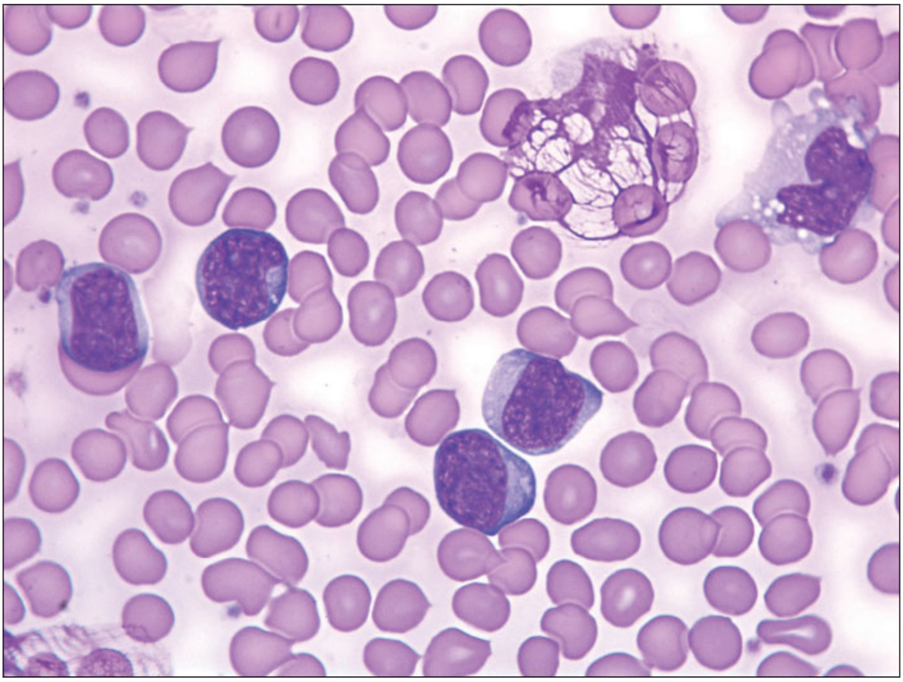


Figure **IIB8-5**

Peripheral blood smear.

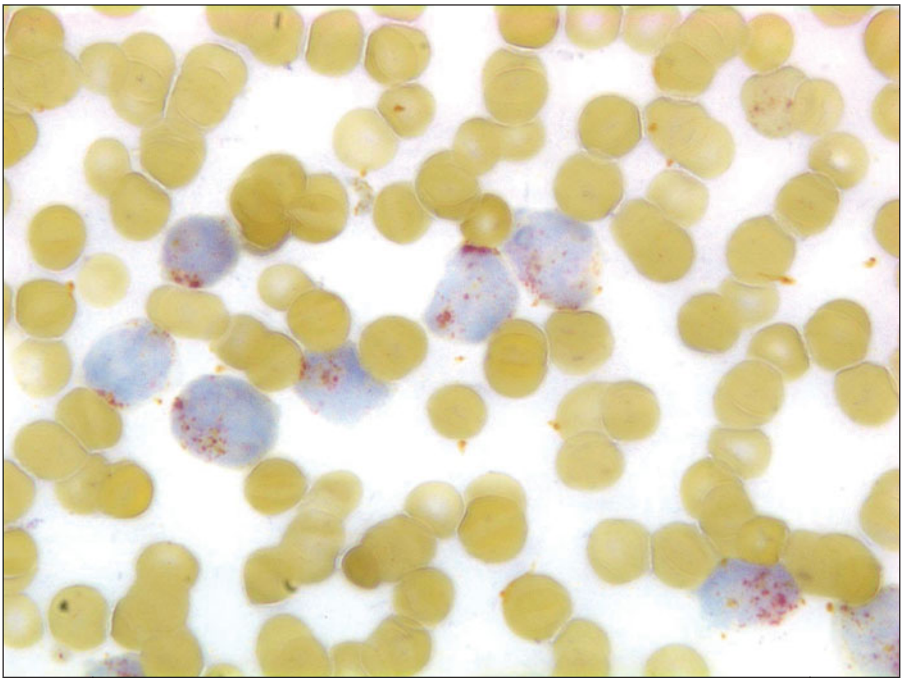


Figure **IIB8-6**

Acid phosphatase stain.

Clinical Features

- Presents with high white count and may have mediastinal mass

Pathology

- Neoplasm of lymphoblasts committed to the T-cell lineage
- Makes up about 15% of childhood ALLs
- Is more common in adolescents than younger children

Laboratory Features

White Blood Cells

- Usually high count

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- Medium-sized blast cells with a high N/C ratio, scant cytoplasm, and usually an irregular nuclear outline
- Chromatin in the nuclei are dispersed to condensed and nucleoli are inconspicuous
- Lymphoblasts are indistinguishable from those of the B-ALL/LBL type
- The number of mitotic figures is higher than in B-ALL/LBL

Cytochemistry

- Show focal acid phosphatase activity

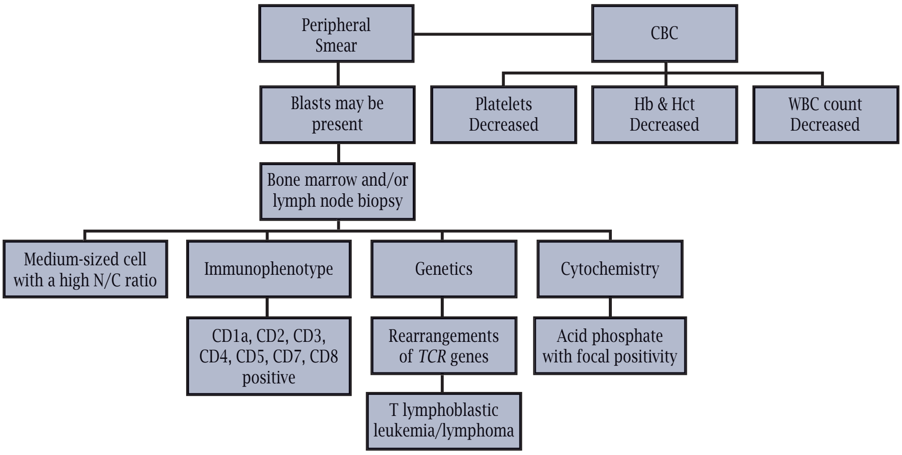
Immunophenotype

- Usually TdT positive and may express CD1a, CD2, CD3, CD4, CD5, CD7, and CD8
- CD7 and cCD3 are expressed the strongest

Genetics

- Most cases show rearrangements of the *TCR* gene
- About 20% of cases also show the presence of *IGH@* gene rearrangements
- 50–70% of cases have an abnormal karyotype involving the alpha and delta TCR loci at 14q11.2, the beta locus at 7q35, and the gamma locus at 7p14–15

Diagnostic Scheme


Peripheral Smear
CBC
Blasts may be present
Platelets Decreased
Hb & Hct Decreased
WBC count Decreased
Bone marrow and/or lymph node biopsy
Medium-sized cell with a high N/C ratio
Immunophenotype
Genetics
Cytochemistry
CD1a, CD2, CD3, CD4, CD5, CD7, CD8 positive
Rearrangements of TCR genes
Acid phosphate with focal positivity
T lymphoblastic leukemia/lymphoma

CHAPTER 9

Mature B-cell Neoplasms

CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

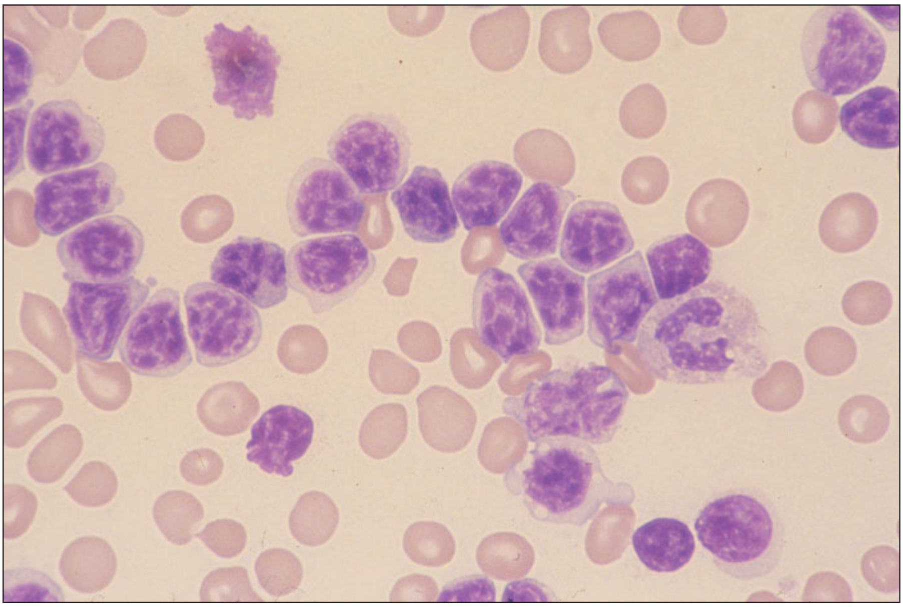


Figure IIB9-1

Peripheral blood smear.

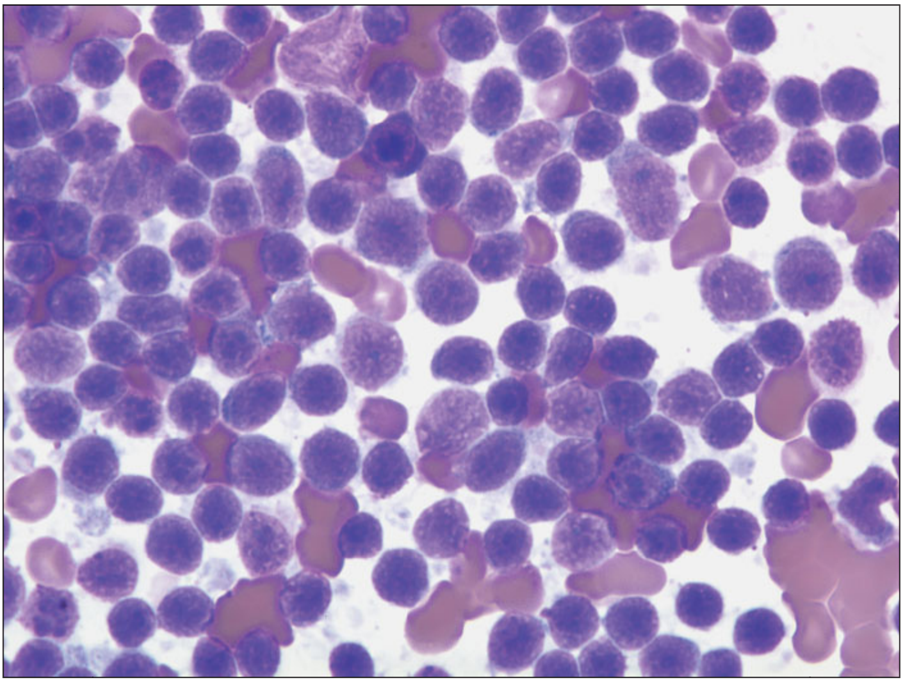


Figure IIB9-2

Bone marrow smear.

Clinical Features

- Occurs most frequently in persons older than 50 years and accounts for about 30% of leukemias
- Enlargement of superficial lymph nodes is common
- With disease progression, hepatosplenomegaly develops
- Infections are frequent
- May develop a secondary warm autoimmune hemolytic anemia
- Some patients are asymptomatic

Pathology

- Proliferation and accumulation of B lymphocytes
- Monoclonal B-cell population with low-density surface immunoglobulin
- Approximately 3.5% of chronic lymphocytic leukemia cases transform into a more aggressive stage of high-grade large-cell lymphoma cells

Laboratory Features

White Blood Cells

- Increased to 20–200 × 10^9/L
- Absolute lymphocytosis – >5.0 × 10^9/L
- Typical, small lymphocytes, with a hypermature-appearing nucleus
- Smudge cells present
- <2% prolymphocytes – increased prolymphocytes indicates more aggressive course
- Larger cells may be seen in Richter's syndrome

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Normal
- Often decreased with disease progression

Bone Marrow

- Replacement by lymphocytes
- <2% prolymphocytes

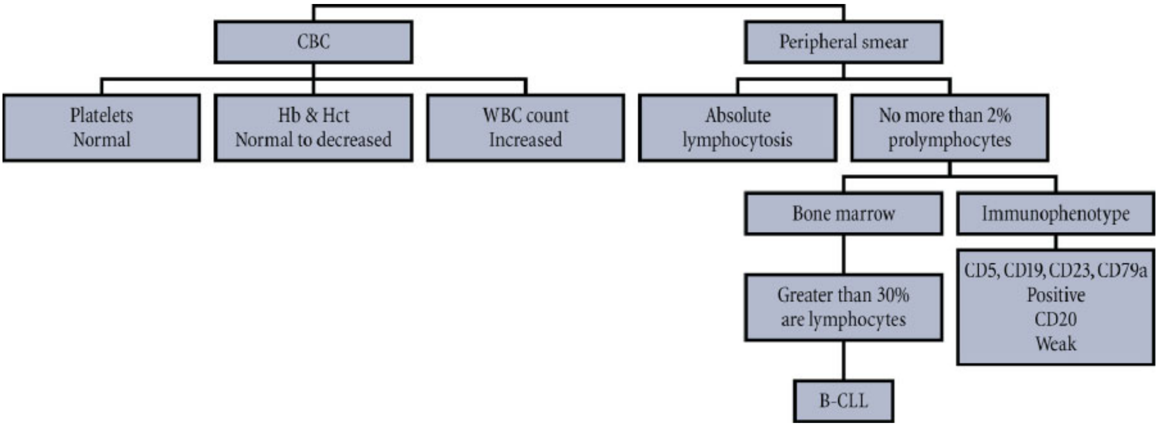
Immunophenotype

- CD5, CD19, CD23, and CD79a positive
- CD20 and sIg weak

Genetics

- Chromosomal abnormalities include:
  - 13q deletion, which is the most common
  - Trisomy 12, 17p deletion and 11q deletion

Diagnostic Scheme


CBC
Peripheral smear
Platelets Normal
Hb & Hct Normal to decreased
WBC count Increased
Absolute lymphocytosis
No more than 2% prolymphocytes
Bone marrow
Immunophenotype
Greater than 30% are lymphocytes
CD5, CD19, CD23, CD79a Positive CD20 Weak
B-CLL

B-CELL PROLYMPHOCYTIC LEUKEMIA

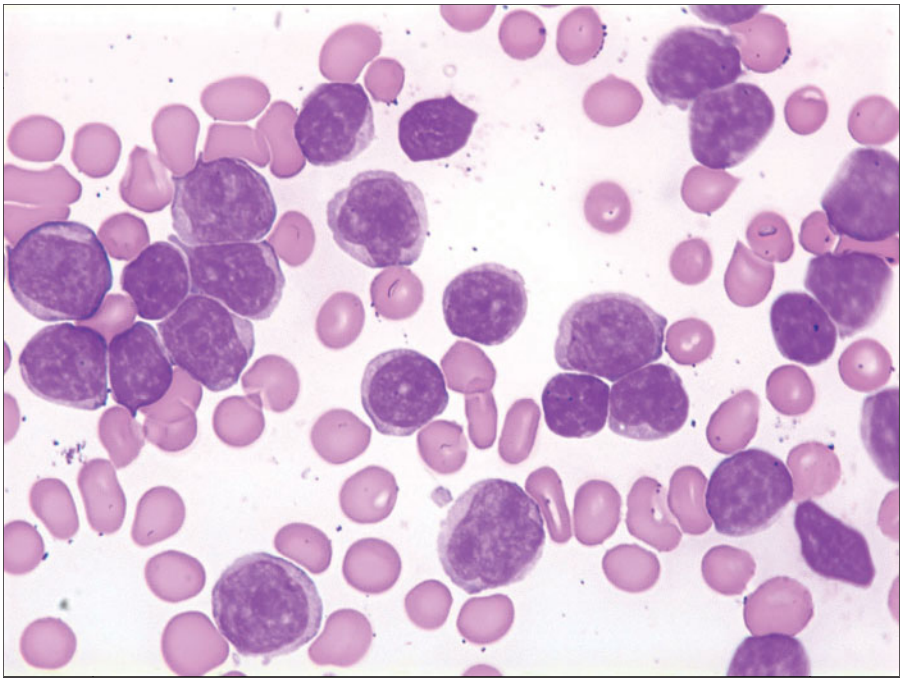


Figure IIB9-3

Peripheral blood smear.

Clinical Features

- Systemic symptoms such as weakness, fatigue, weight loss, fever, and possibly abdominal pain are seen
- Absent or minimal lymphadenopathy
- Massive splenomegaly, hepatomegaly, and bone marrow infiltration

Pathology

- Disease of mature B cells (about 2% of cases of T cells)
- Median age of occurrence is 60 years, with a male predominance

Laboratory Features

White Blood Cells

- Typically >100 × 10^9/L
- >55% prolymphocytes
- Cells contain a large, vesicular nucleolus, condensed nuclear chromatin, and have lower N/C ratio

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- Same types of prolymphocytes seen in the peripheral blood

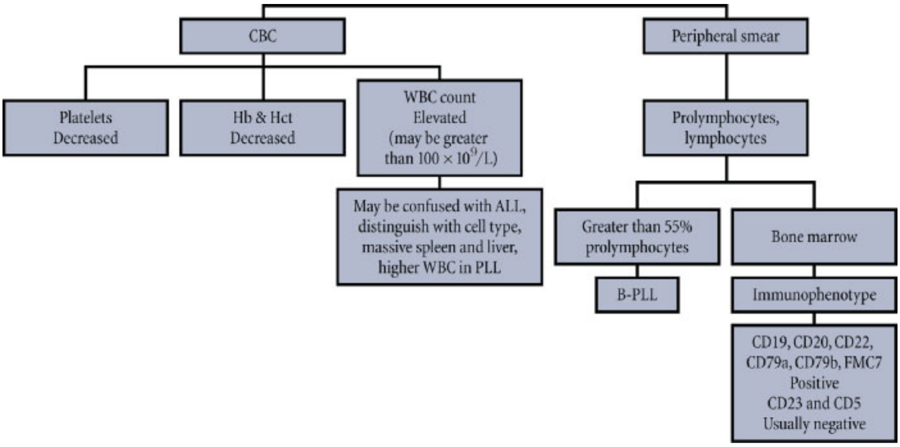
Immunophenotype

- CD19, CD20, CD22, CD79a and b, FMC7 and sIg positive
- CD5 and CD23 positive in less than one-third of the cases

Genetics

- Exhibit heavy and light chain Ig gene rearrangements
- Cells express much more sIg than do chronic lymphocytic leukemia cells
- Chromosomal abnormality t(11;14), del(17p) and del at 13q14

Diagnostic Scheme


CBC
Peripheral smear
Platelets Decreased
Hb & Hct Decreased
WBC count Elevated (may be greater than 100 × 10^9/L)
May be confused with ALL, distinguish with cell type, massive spleen and liver, higher WBC in PLL
Prolymphocytes, lymphocytes
Greater than 55% prolymphocytes
B-PLL
Bone marrow
Immunophenotype
CD19, CD20, CD22, CD79a, CD79b, FMC7 Positive
CD23 and CD5 Usually negative

HAIRY CELL LEUKEMIA

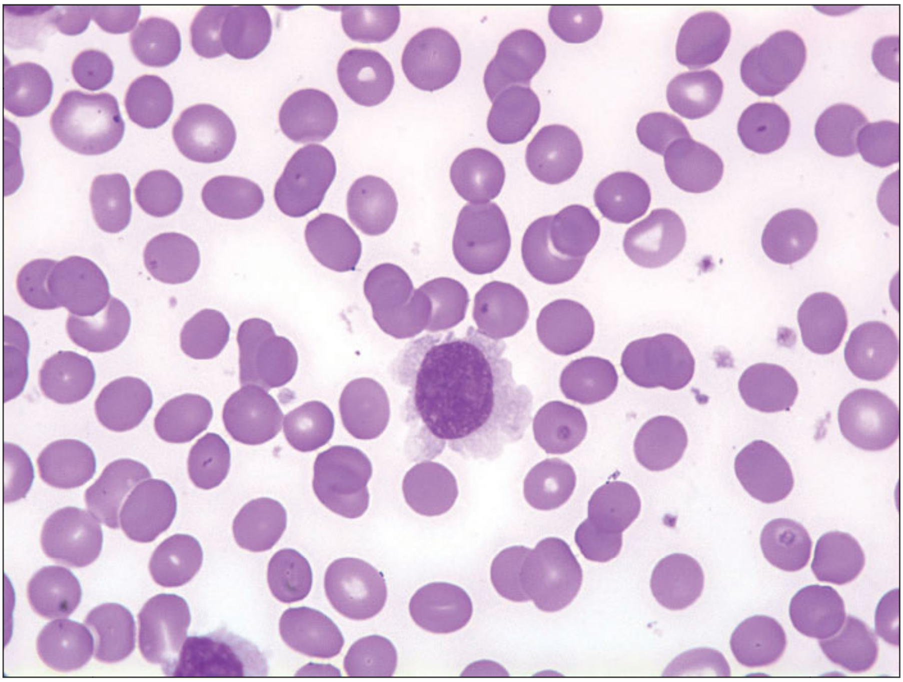


Figure IIB9-4

Peripheral blood smear.

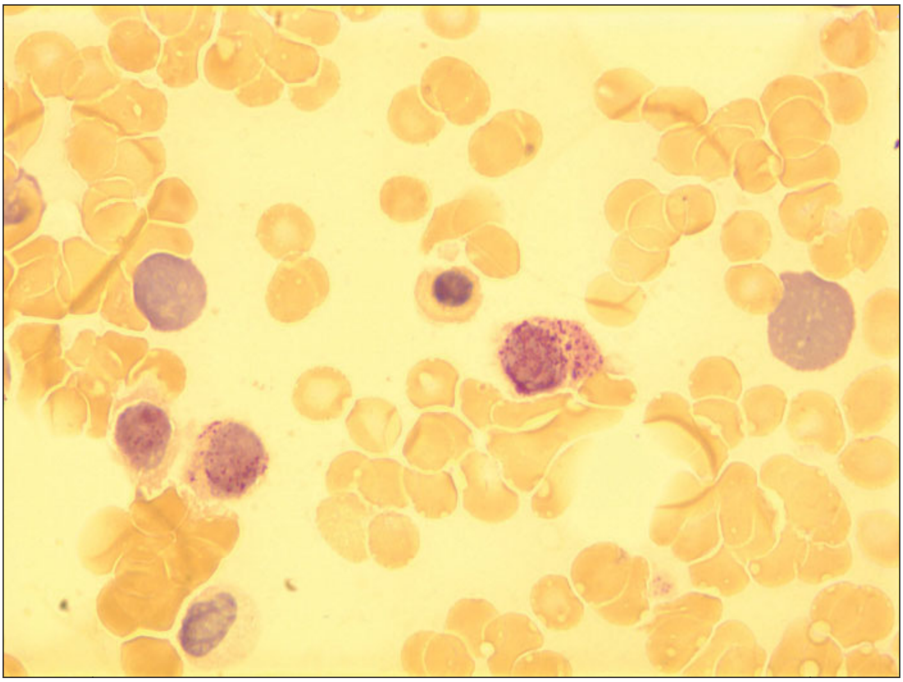


Figure IIB9-5

TRAP stain.

Clinical Features

- Weakness and fatigue
- Easy bruising and bleeding tendency
- Recurrent infections
- Hepatomegaly and splenomegaly

Pathology

- B-cell disease
- Male predominance (5:1)
- Median age of onset is about 50 years

Laboratory Features

White Blood Cells

- Usually decreased
- Presence of hairy cells
- Monocytopenia

Red Blood Cells

- Moderate normocytic/normochromic anemia

Platelets

- $<100 \times 10^9$/L in 50% of patients

Bone Marrow

- Cannot be aspirated in more than half of the cases because of reticulin fibers
- Small- to medium-sized lymphoid cells with oval or bean-shaped nucleus
- The pale blue cytoplasm is abundant and has “hairy” projections

Cytochemistry

- Tartrate-resistant acid phosphatase positive
- Specific esterase (Naphthol AS-D chloroacetate esterase) and myeloperoxidase reactions are negative

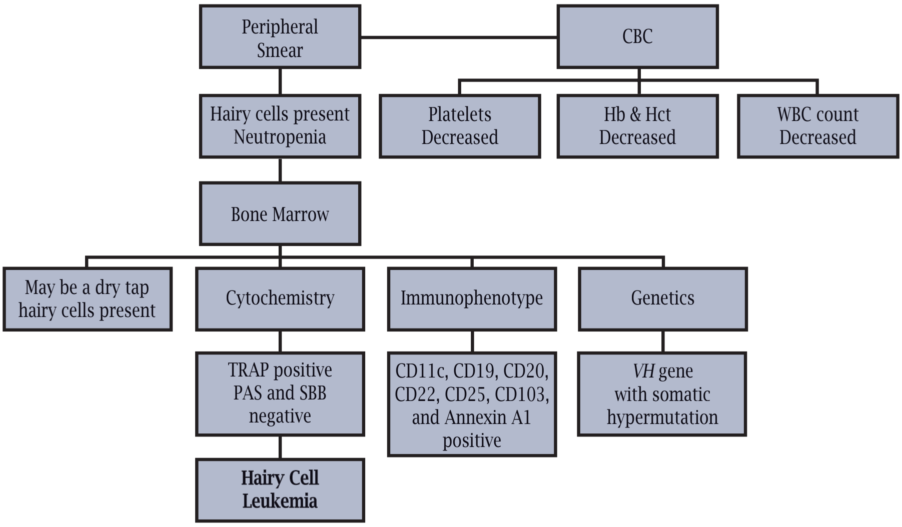
Immunophenotype

- CD103, CD20, CD19, CD22, CD11c, CD25, and Annexin A1 positive

Genetics

- About 85% of cases demonstrate *VH* genes with somatic hypermutation

Diagnostic Scheme


Peripheral Smear
CBC
Hairy cells present Neutropenia
Platelets Decreased
Hb & Hct Decreased
WBC count Decreased
Bone Marrow
May be a dry tap hairy cells present
Cytochemistry
Immunophenotype
Genetics
TRAP positive PAS and SBB negative
CD11c, CD19, CD20, CD22, CD25, CD103, and Annexin A1 positive
VH gene with somatic hypermutation
Hairy Cell Leukemia

PLASMA CELL NEOPLASMS

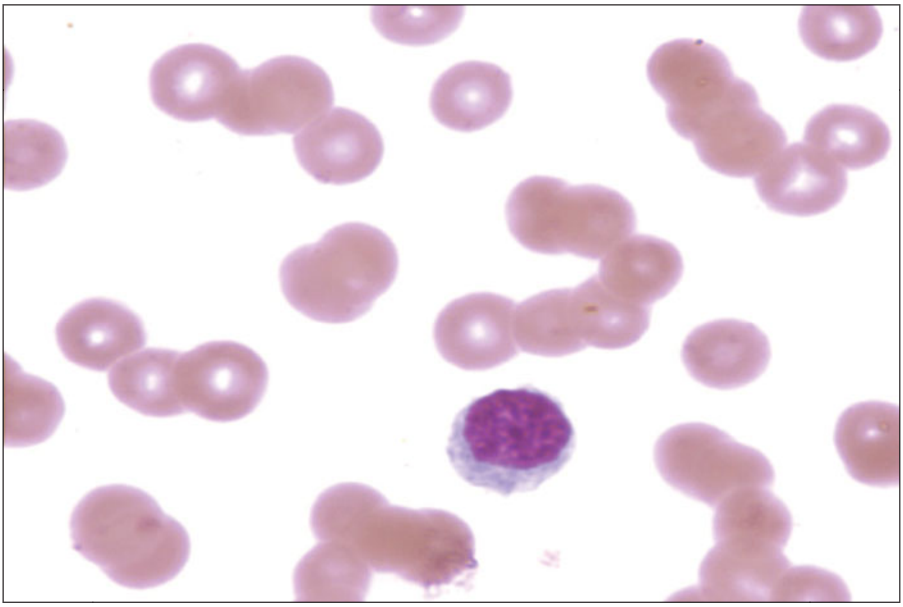


Figure IIB9-6

Peripheral blood smear.

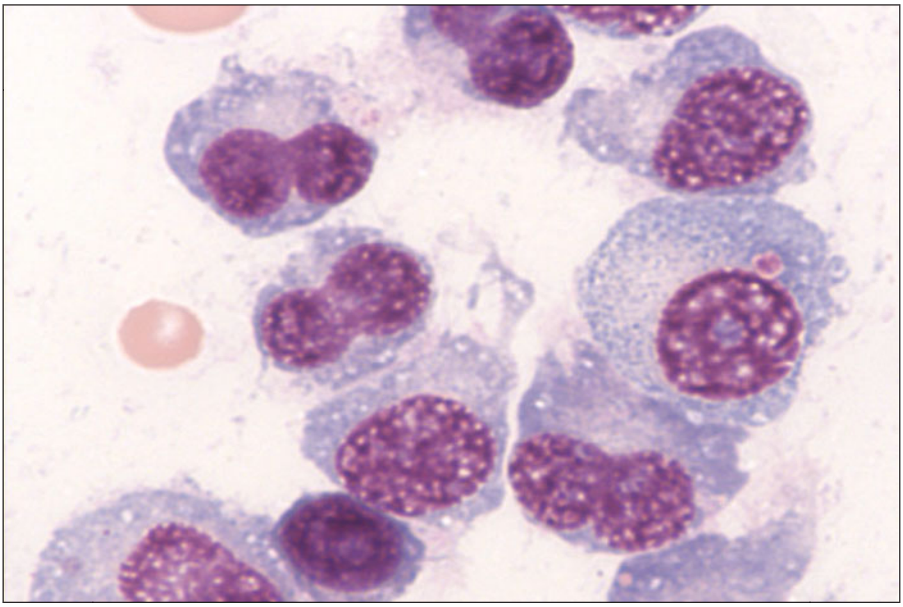


Figure IIB9-7

Bone marrow smear.

Clinical Features

- Fatigue and generalized aching
- Bone pain with lytic lesions
- Neurologic abnormalities
- Infections and renal failure

Pathology

- Median age of onset is about 65 years of age
- Malignant proliferation of a clone of plasma cells
- Plasma cells secrete complete or incomplete monoclonal immunoglobulins
- Prolonged excretion of Bence Jones protein in the urine often results in renal failure
- Increased susceptibility to infections and bleeding problems

Laboratory Features

White Blood Cells

- Count is usually normal
- Plasma cells may be present

Red Blood Cells

- Normocytic/normochromic anemia
- Rouleaux
- Increased sedimentation rate

Platelets

- Normal to decreased
- Abnormal function

Bone Marrow

- >10% plasmacytosis and usually >30%
- Myeloma cells are present
- Single eccentrically placed nucleus
- Nucleoli may be seen in finely divided chromatin
- Various types of inclusions may be present

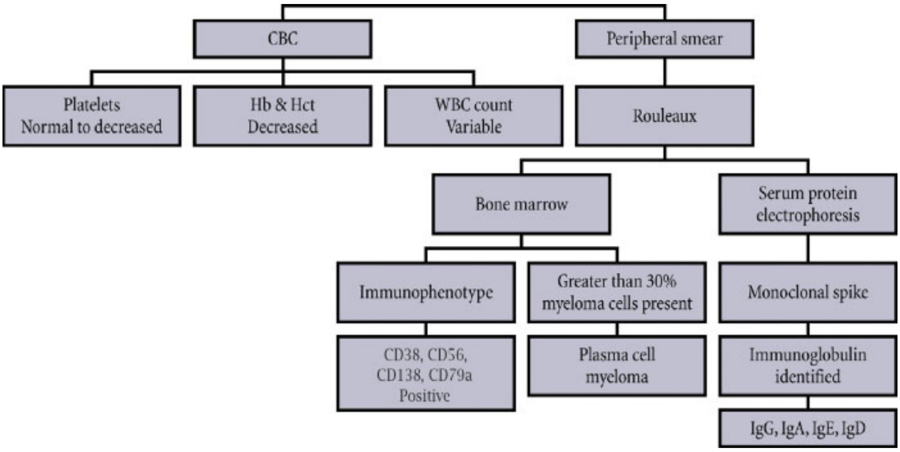
Immunophenotype

- CD38, CD56, CD79a, and CD138 positive

Genetics

- High load of *IGHV* gene somatic hypermutation
- Heavy and light chains of the immunoglobins are clonally rearranged

Diagnostic Scheme


CBC
Peripheral smear
Platelets Normal to decreased
Hb & Hct Decreased
WBC count Variable
Rouleaux
Bone marrow
Serum protein electrophoresis
Immunophenotype
Greater than 30% myeloma cells present
Monoclonal spike
CD38, CD56, CD138, CD79a Positive
Plasma cell myeloma
Immunoglobulin identified
IgG, IgA, IgE, IgD

PLASMA CELL LEUKEMIA

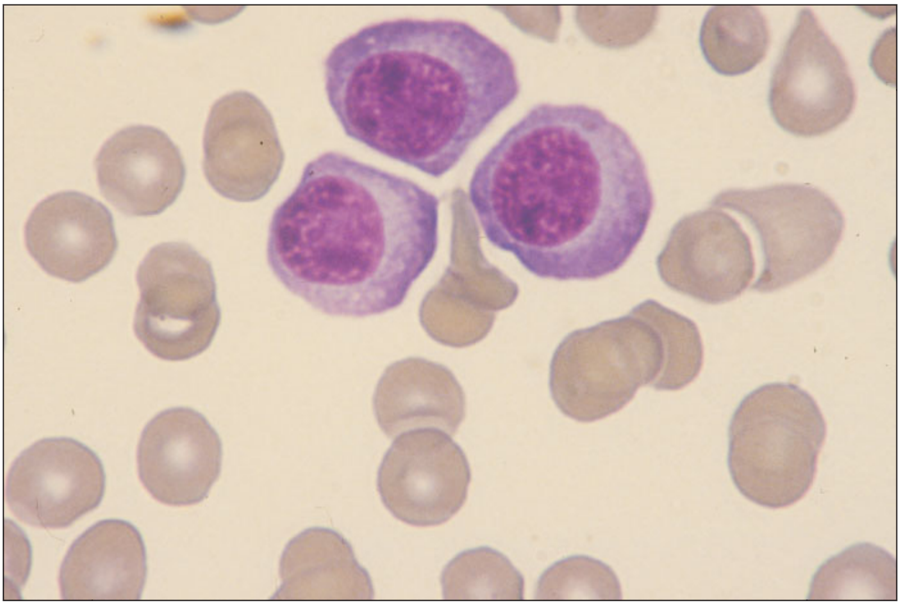


Figure IIB9-8

Peripheral blood smear.

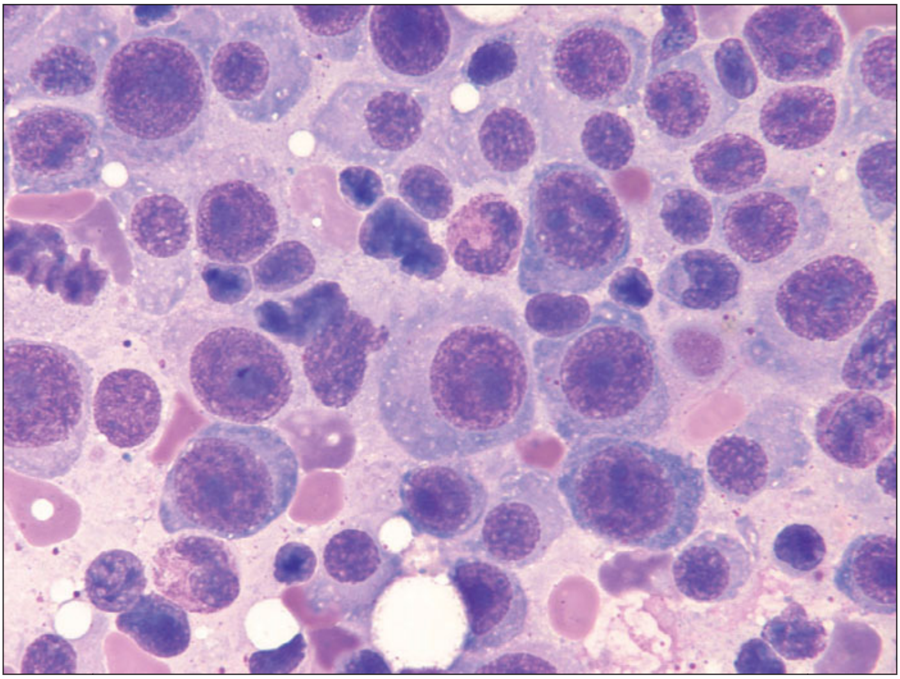


Figure IIB9-9

Bone marrow smear.

Clinical Features

- Hepatosplenomegaly
- Lymphadenopathy
- Lytic bone lesions are frequently seen
- Severe anemia

Pathology

- Primary plasma cell leukemia demonstrates circulating myeloma cells at the time of diagnosis
- Secondary plasma cell leukemia represents the advanced stage of myeloma (a leukemic phase), which occurs as a terminal event in about 1–5% of cases

Laboratory Features

White Blood Cells

- Plasma cells in the peripheral blood – 2×10^9/L or 20%
- Leukocytosis

Red Blood Cells

- Severe normocytic/normochromic anemia
- Rouleaux

Platelets

- Decreased

Bone Marrow

- Diffuse plasma cell infiltration is variable but may be as high as 90%
- Plasma cells are well differentiated
- Binucleated plasma cells may be present

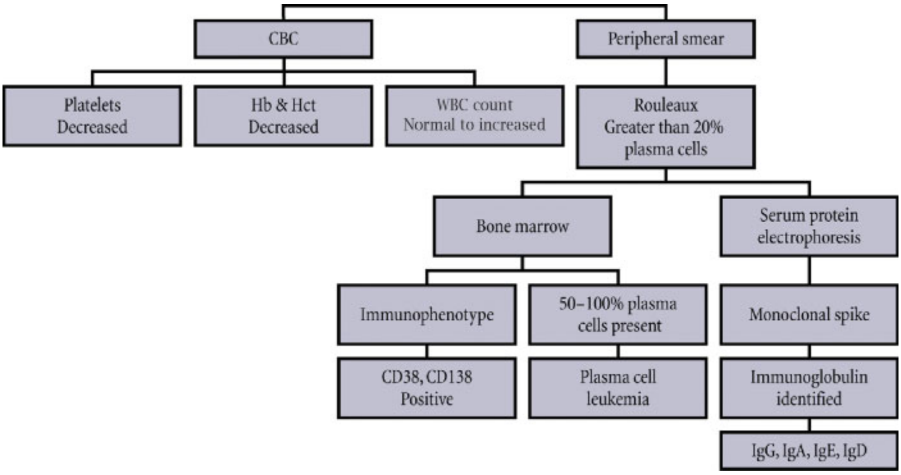
Immunophenotype

- CD38, CD138, and CD79a positive

Genetics

- High load of *IGHV* gene somatic hypermutation
- Heavy and light chains of the immunoglobins are clonally rearranged

Diagnostic Scheme


CBC
Peripheral smear
Platelets Decreased
Hb & Hct Decreased
WBC count Normal to increased
Rouleaux Greater than 20% plasma cells
Bone marrow
Serum protein electrophoresis
Immunophenotype
50–100% plasma cells present
Monoclonal spike
CD38, CD138 Positive
Plasma cell leukemia
Immunoglobulin identified
IgG, IgA, IgE, IgD

EXTRANODAL MARGINAL ZONE LYMPHOMA OF MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT LYMPHOMA)

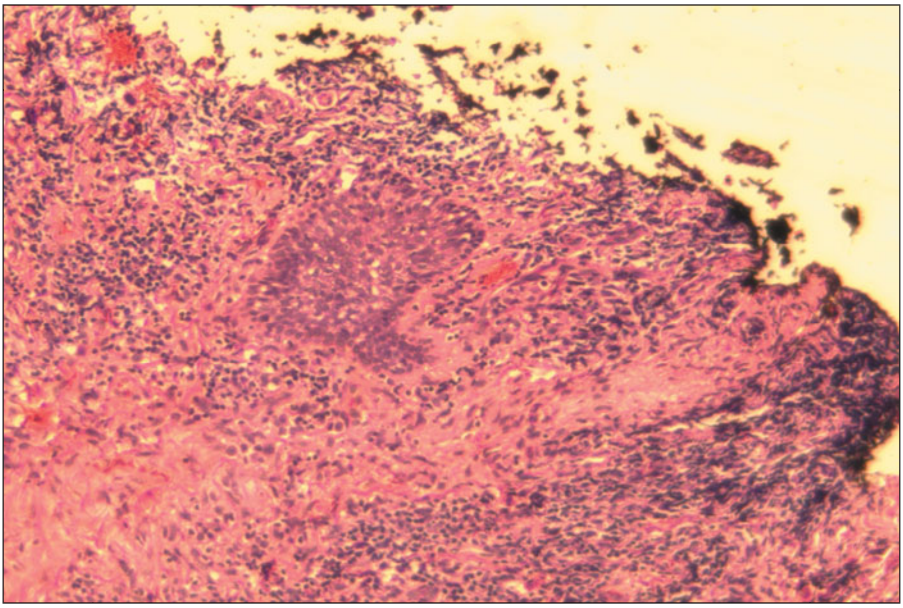


Figure IIB9-10

Tissue section.

Clinical Features

- Occurs in extranodal sites such as the stomach, salivary glands, and thyroid
- A minor number of cases have bone marrow involvement

Pathology

- Malignant cells arise from the B cells localized in the marginal zone of the follicle
- Tends to be indolent and remain localized for long periods
- Gastric MALT may be associated with *Helicobacter pylori* infections
- Female predominance

Laboratory Findings

Cell Types

- Variable-sized lymphocytes
- Centrocyte-like cells
- Monocytoid B cells

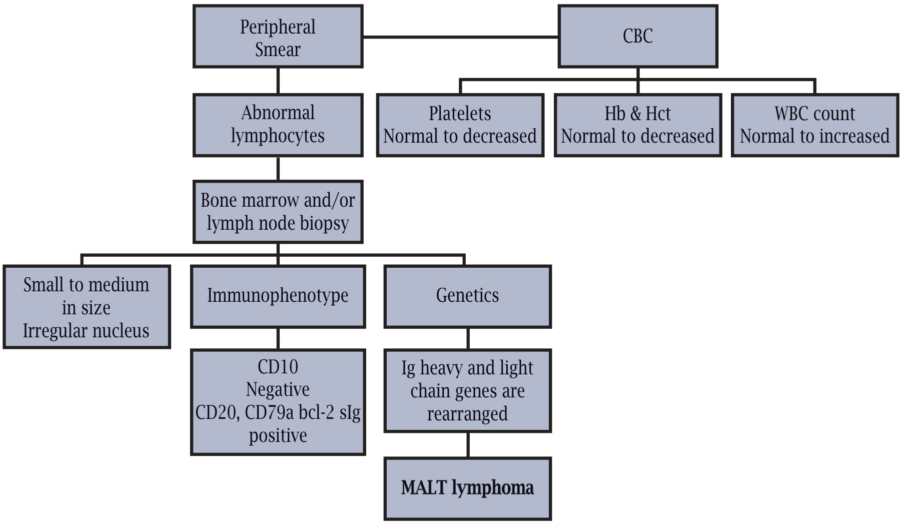
Immunophenotype

- CD20, CD79a, bcl-2, sIg, some cIg positive
- CD5, CD10, and CD23 negative

Genetics

- Oncogenes may be implicated
- Chromosomal abnormalities include t(11;14) and rearranged *bcl-1* gene

Diagnostic Scheme


Peripheral Smear
CBC
Abnormal lymphocytes
Platelets Normal to decreased
Hb & Hct Normal to decreased
WBC count Normal to increased
Bone marrow and/or lymph node biopsy
Small to medium in size Irregular nucleus
Immunophenotype
Genetics
CD10 Negative CD20, CD79a bcl-2 sIg positive
Ig heavy and light chain genes are rearranged
MALT lymphoma

FOLLICULAR LYMPHOMA

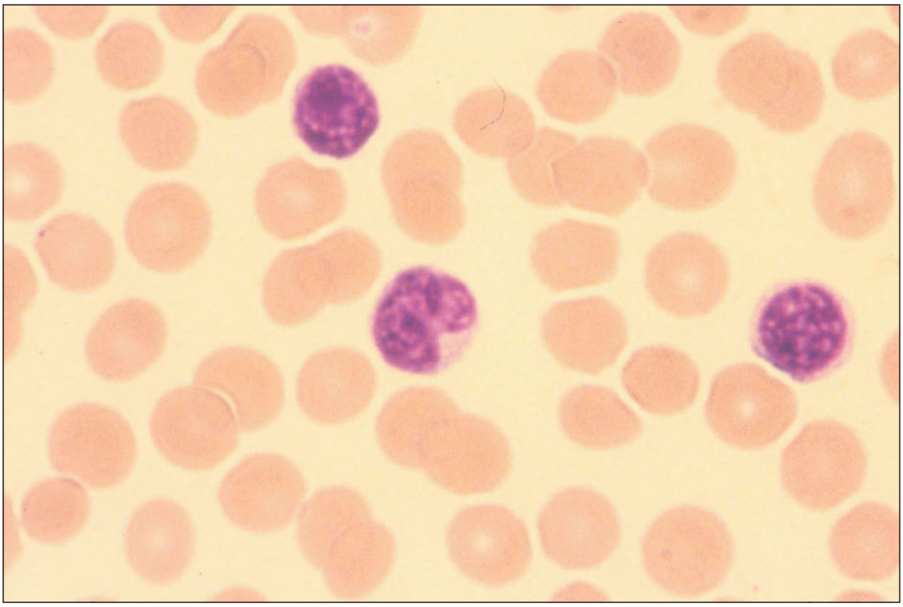


Figure IIB9-11

Peripheral blood smear—small follicular cell.

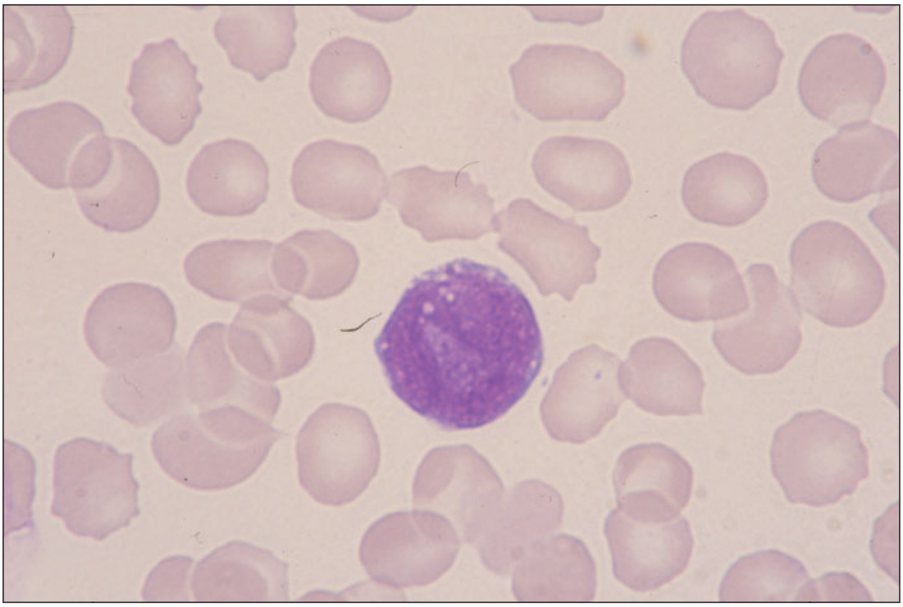


Figure IIB9-12

Peripheral blood smear—large follicular cell.

Clinical Features

- Adenopathy
- Splenomegaly

Pathology

- Usually occurs in older males
- Arises from follicular structure
- Indolent course

Laboratory Features

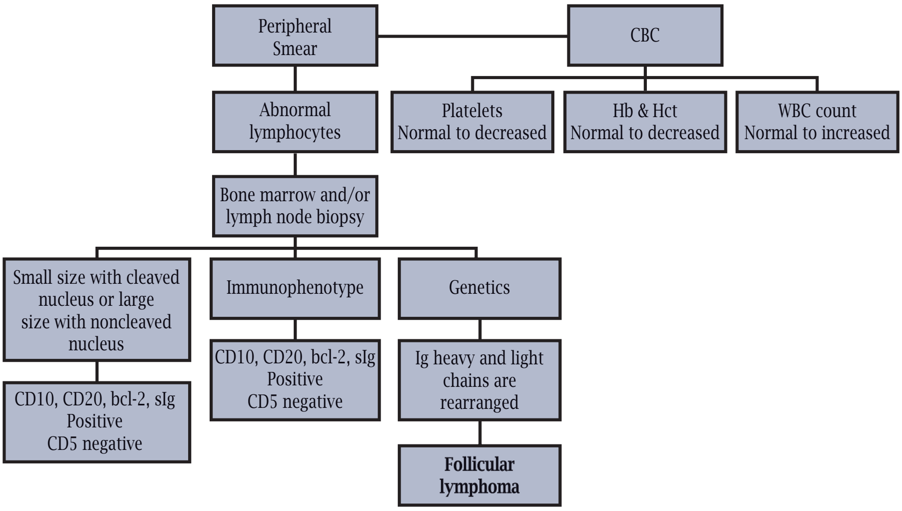
Cell Types

- Based on the origin of the malignancy in the follicle
  - Small cleaved follicle center cell (centerocyte)
    - Scant cytoplasm
  - Large follicle center cell (centroblasts)
    - Basophilic cytoplasm
  - Follicular pattern

Immunophenotype

- Bcl-2, CD10, CD20, and sIg positive
- CD23 plus/minus
- CD5 negative

Diagnostic Scheme


Peripheral Smear
CBC
Abnormal lymphocytes
Platelets Normal to decreased
Hb & Hct Normal to decreased
WBC count Normal to increased
Bone marrow and/or lymph node biopsy
Small size with cleaved nucleus or large size with noncleaved nucleus
Immunophenotype
Genetics
CD10, CD20, bcl-2, sIg Positive CD5 negative
CD10, CD20, bcl-2, sIg Positive CD5 negative
Ig heavy and light chains are rearranged
Follicular lymphoma

MANTLE CELL LYMPHOMA

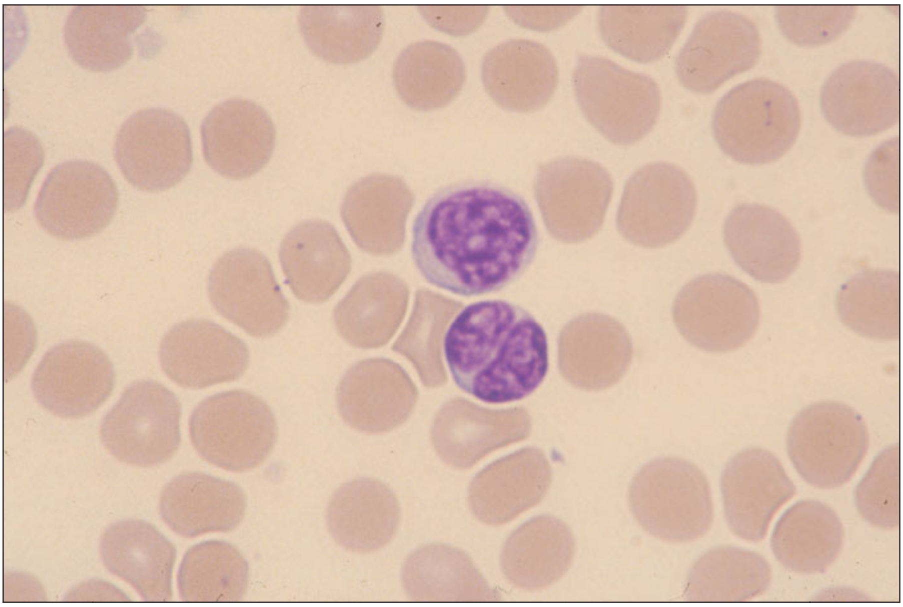


Figure IIB9-13

Peripheral blood smear.

Clinical Features

- Adenopathy

Pathology

- Arises from the mantle cell of primary and secondary lymph node follicles
- Moderately aggressive

Laboratory Features

Cell Type

- Small- to medium-sized cell
- Irregular nucleus
- Scant cytoplasm

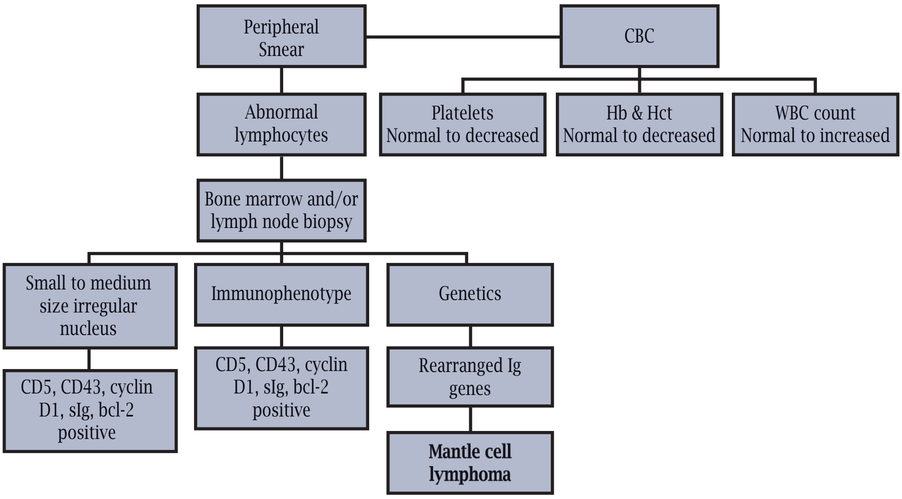
Immunophenotype

- CD19, CD20, and CD22 lymphoid antigens present
- CD43, cyclin D1, sIg, CD5, bcl-2 positive
- cIg, CD10, and CD23

Genetics

- Chromosomal abnormalities include: t(11;14) and rearranged *bcl-1* gene
- Oncogenes may be implicated

Diagnostic Scheme


Peripheral Smear
CBC
Abnormal lymphocytes
Platelets Normal to decreased
Hb & Hct Normal to decreased
WBC count Normal to increased
Bone marrow and/or lymph node biopsy
Small to medium size irregular nucleus
Immunophenotype
Genetics
CD5, CD43, cyclin D1, sIg, bcl-2 positive
CD5, CD43, cyclin D1, sIg, bcl-2 positive
Rearranged Ig genes
Mantle cell lymphoma

DIFFUSE LARGE B-CELL LYMPHOMA, NOT OTHERWISE SPECIFIED

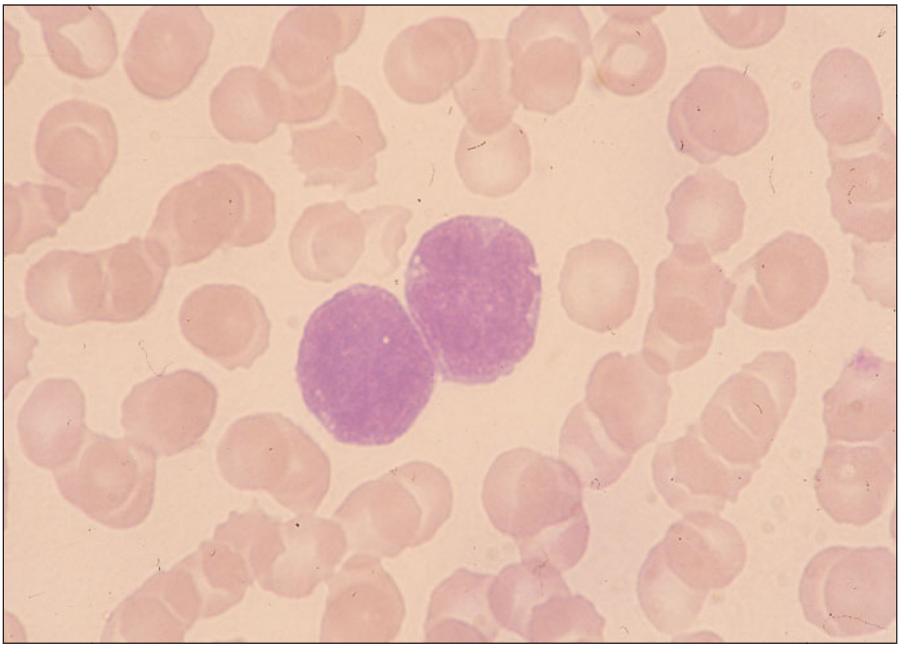


Figure IIB9-14

Peripheral blood smear.

Clinical Features

- Adenopathy
- Hepatosplenomegaly

Pathology

- May be associated with viral infections
- Rapidly enlarging tumor
- Usually occurs in older males

Laboratory Findings

Cell Type

- Sheets of large heterogeneous lymphocytes with variable cytoplasm

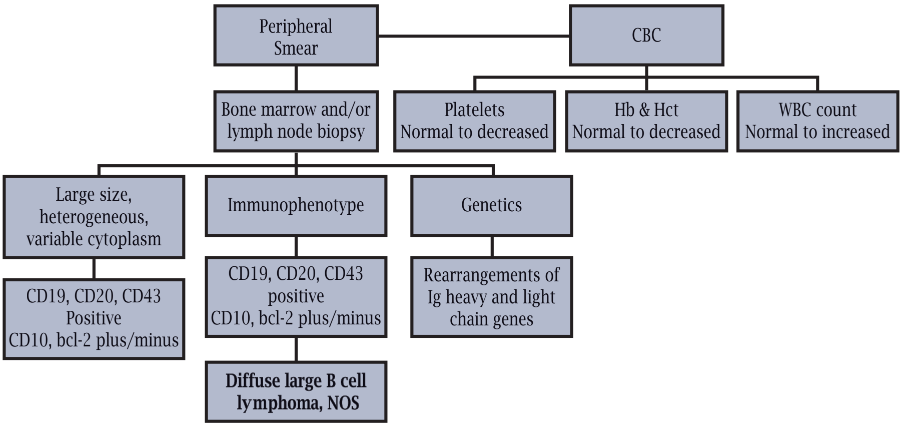
Immunophenotype

- CD19, CD20, and CD43 positive
- CD10, bcl-2 plus/minus

Genetics

- Chromosomal abnormalities may be observed
- Oncogenes may be implicated

Diagnostic Scheme


Peripheral Smear
CBC
Bone marrow and/or lymph node biopsy
Platelets Normal to decreased
Hb & Hct Normal to decreased
WBC count Normal to increased
Large size, heterogeneous, variable cytoplasm
Immunophenotype
Genetics
CD19, CD20, CD43 Positive CD10, bcl-2 plus/minus
CD19, CD20, CD43 positive CD10, bcl-2 plus/minus
Rearrangements of Ig heavy and light chain genes
Diffuse large B cell lymphoma, NOS

BURKITT LYMPHOMA

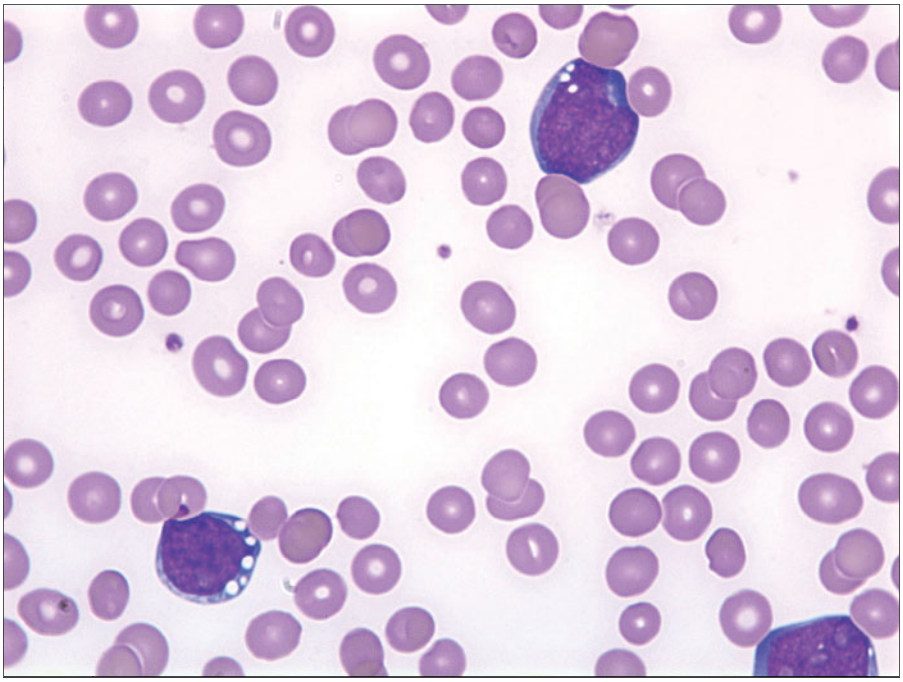


Figure IIB9-15

Peripheral blood smear.

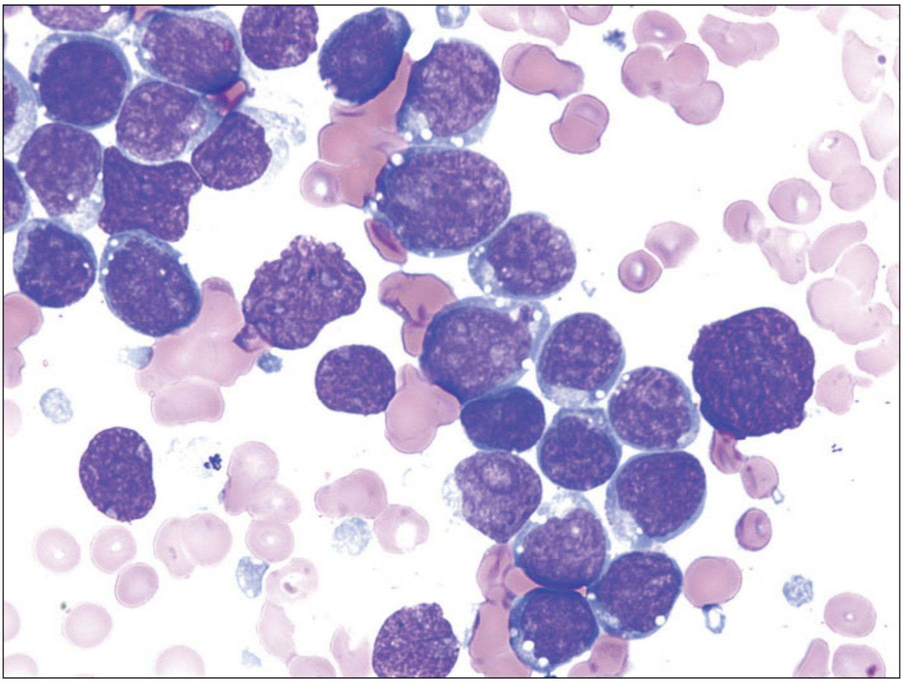


Figure IIB9-16

Bone marrow smear.

Clinical Features

- Adenopathy, but may have extranodal involvement
- Rapidly growing mass may be present, especially in the jaw bone

Pathology

- Usually occurs in children or young adults
- Viruses such as Epstein–Barr virus and HIV may be associated
- Diffuse, not follicular, lymphoma
- Undifferentiated B cells of unknown origin
- Highly aggressive

Laboratory Features

Cell Types

- Monomorphic medium-sized cell
- Round nucleus
- 2–5 prominent nucleoli
- Moderate basophilic cytoplasm with vacuoles

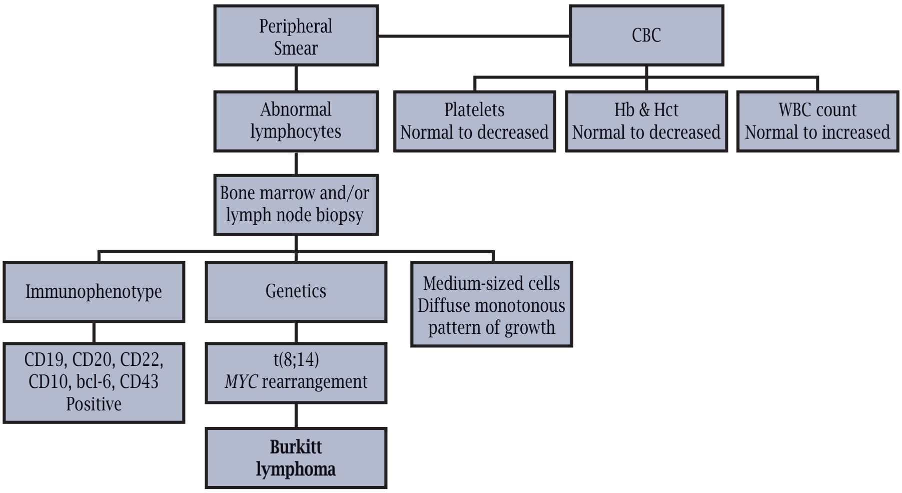
Immunophenotype

- CD19, CD20, and CD22 present
- sIgM, CD10, CD43, and bcl-6 positive
- CD5, CD23, bcl-2 negative

Genetics

- Oncogenes may be implicated
- *IgH* and *IgL* genes are rearranged
- t(8;14)

Diagnostic Scheme


Peripheral Smear
CBC
Abnormal lymphocytes
Platelets Normal to decreased
Hb & Hct Normal to decreased
WBC count Normal to increased
Bone marrow and/or lymph node biopsy
Immunophenotype
Genetics
Medium-sized cells Diffuse monotonous pattern of growth
CD19, CD20, CD22, CD10, bcl-6, CD43 Positive
t(8;14) *MYC* rearrangement
Burkitt lymphoma

CHAPTER 10

Mature T- and NK-cell Neoplasms

T-CELL LARGE GRANULAR LYMPHOCYTIC LEUKEMIA

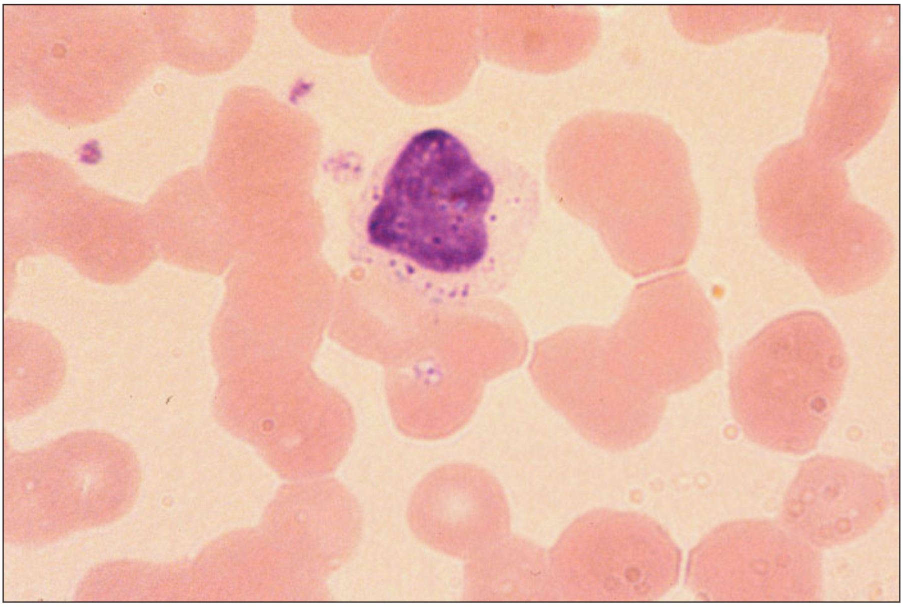


Figure IIB10-1

Peripheral blood smear.

Clinical Features

- Some patients are asymptomatic
- Recurrent infections
- Rheumatoid arthritis
- Splenomegaly

Pathology

- Clonal disease may arise from either of the two large granular lymphocyte lineages: T-large granular lymphocyte leukemia (T-LGL) and natural killer-large granular (NK-LGL) lymphocytic leukemia
- Defects in programmed cell death
- Viral infections may be an initial stimulus

Laboratory Features

White Blood Cells

- Persistent neutropenia
- Lymphocytosis in the range of 4.0–10.0 × 10^9/L
- Presence of large granular lymphocytes

Red Blood Cells

- May have a macrocytic anemia

Platelets

- Normal to decreased

Bone Marrow

- Lymphocytic infiltration

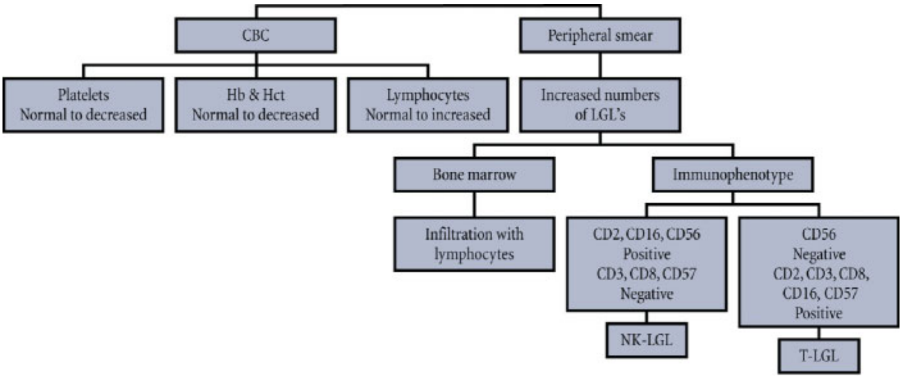
Immunophenotype

- CD3 and CD8 positive

Genetics

- *TRG@* gene is rearranged
- No unique karyotypic abnormalities

Diagnostic Scheme


CBC
Peripheral smear
Platelets Normal to decreased
Hb & Hct Normal to decreased
Lymphocytes Normal to increased
Increased numbers of LGL's
Bone marrow
Immunophenotype
Infiltration with lymphocytes
CD2, CD16, CD56 Positive CD3, CD8, CD57 Negative
CD56 Negative CD2, CD3, CD8, CD16, CD57 Positive
NK-LGL
T-LGL

ADULT T-CELL LEUKEMIA/LYMPHOMA

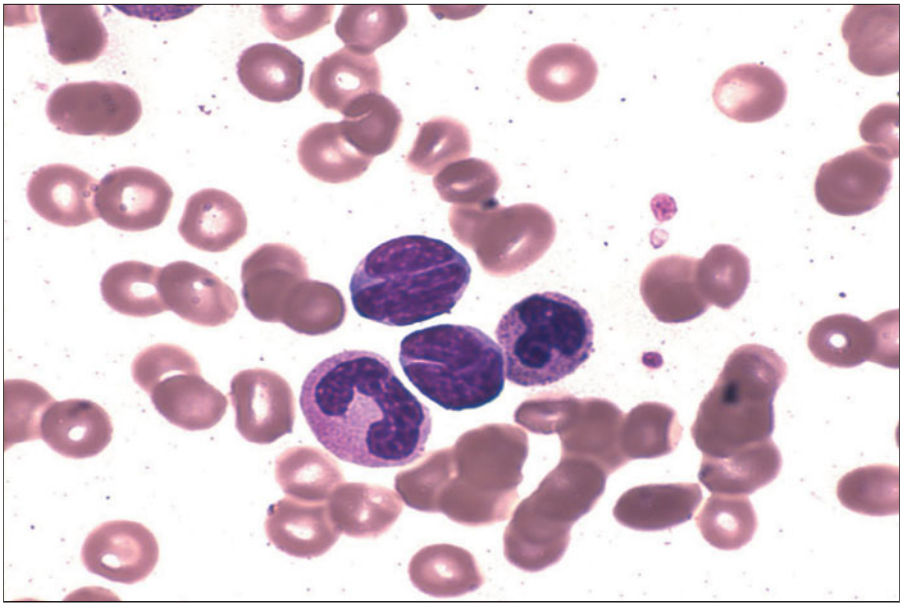


Figure IIB10-2

Peripheral blood smear.

Clinical Features

- Evolves rapidly
- Skin lesions
- Hepatosplenomegaly
- Adenopathy

Pathology

- Only chronic leukemia where the virus has been demonstrated (human T-cell lymphotropic virus type 1)
- Invasion of cells by the virus causes cell proliferation

Laboratory Features

White Blood Cells

- May be only a few abnormal cells in the peripheral blood
- Cells have highly convoluted nuclei with deep multilobulated indentation
- Cell size and N/C ratio is larger than that of normal lymphocytes

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Normal to decreased

Bone Marrow

- Presence of infiltrates and evidence of bony remodeling and fibrosis

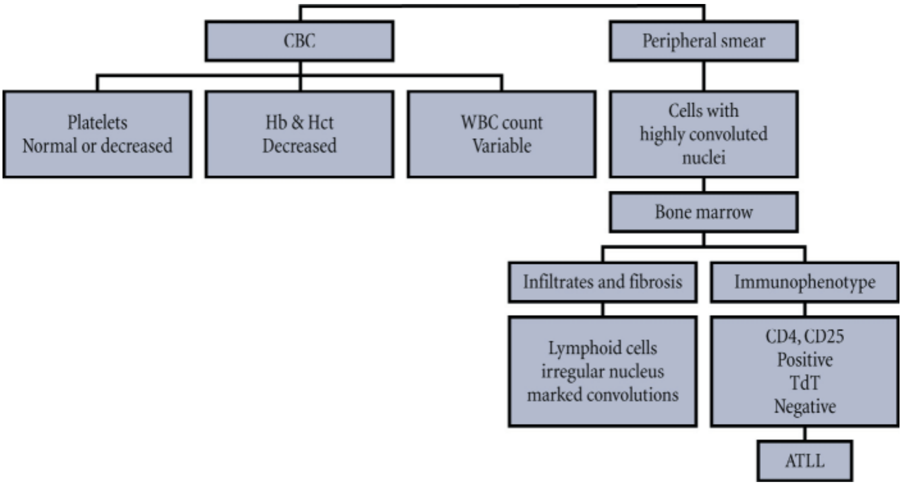
Immunophenotype

- CD4, CD25 positive, and terminal deoxynucleotidyl transferase negative

Genetics

- Rearrangement of T cell receptor (*TCR* gene)

Diagnostic Scheme


CBC
Peripheral smear
Platelets Normal or decreased
Hb & Hct Decreased
WBC count Variable
Cells with highly convoluted nuclei
Bone marrow
Infiltrates and fibrosis
Immunophenotype
Lymphoid cells irregular nucleus marked convolutions
CD4, CD25 Positive TdT Negative
ATLL

SÉZARY SYNDROME

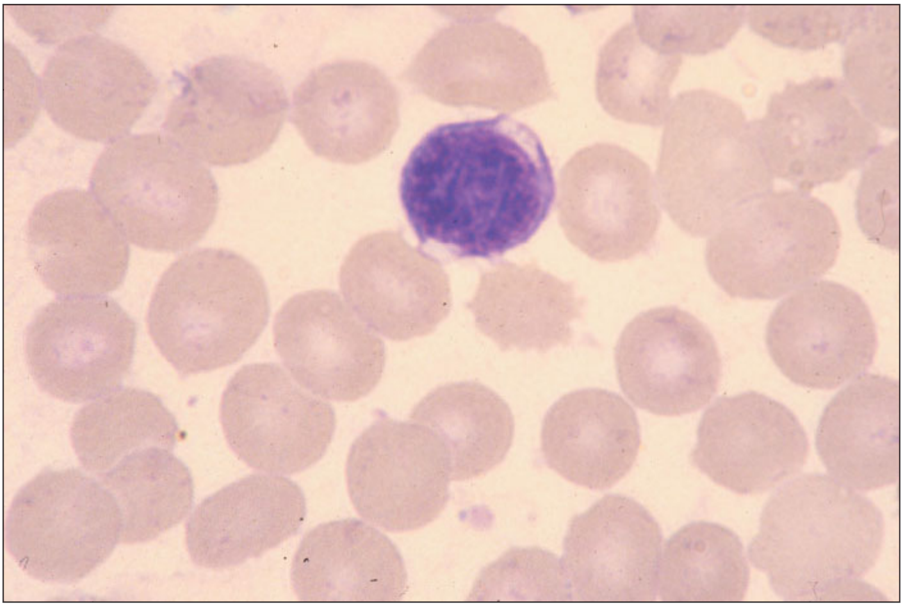


Figure IIB10-3

Peripheral blood smear.

Clinical Features

- Generalized erythroderma
- Pruritus
- Infections

Pathology

- Uncommon malignancy seen more commonly in males (2:1)
- Median age of occurrence is 55 years
- Systemic phase of cutaneous T-cell lymphoma
- Malignant proliferation of T lymphocytes
- Aggressive disease

Laboratory Features

White Blood Cells

- Hyperconvoluted lymphoid cells in blood

Red Blood Cells

- May have a normocytic/normochromic anemia

Platelets

- Normal to decreased

Bone Marrow

- Eosinophilia
- Monocytosis
- Plasmacytosis
- Rare infiltrates of Sézary cells

Cytochemistry

- Focal positivity with acid phosphatase
- Myeloperoxidase, alkaline phosphatase, and specific esterase (chloroacetate esterase) negative

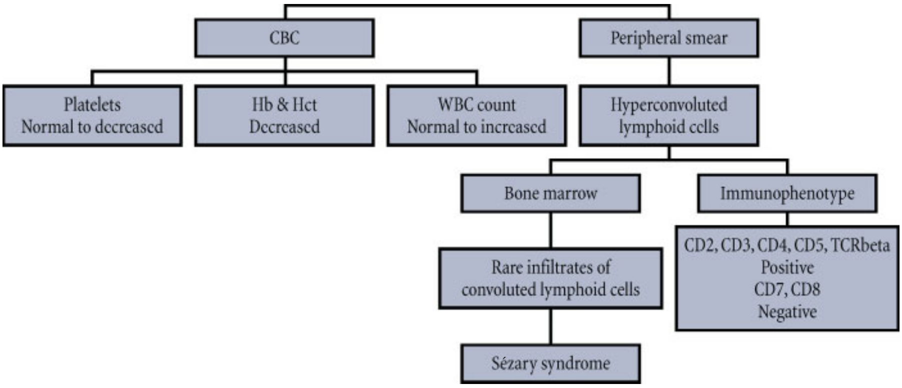
Immunophenotype

- CD2, CD3, CD4, CD5, and TCR beta positive
- CD7 and CD8 negative

Genetics

- T-cell receptor genes are clonally rearranged
- Complex karyotypes with numerical and structural alterations are common

Diagnostic Scheme


CBC
Peripheral smear
Platelets Normal to decreased
Hb & Hct Decreased
WBC count Normal to increased
Hyperconvoluted lymphoid cells
Bone marrow
Immunophenotype
Rare infiltrates of convoluted lymphoid cells
CD2, CD3, CD4, CD5, TCRbeta Positive
CD7, CD8 Negative
Sézary syndrome

CHAPTER 11

Hodgkin Lymphoma

CLASSICAL HODGKIN LYMPHOMA

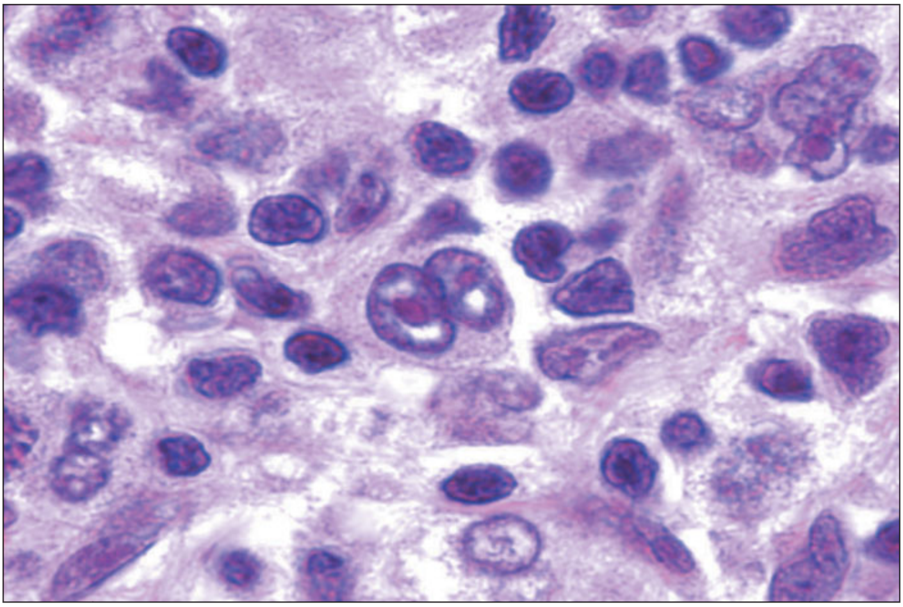


Figure IIB11-1

Lymph node biopsy.

Clinical Features

- Painless lymph node enlargement
- Cough and chest discomfort
- Drenching sweats at night, fever, and weight loss

Pathology

- More common in males than in females
- Peak incidence is about the third decade of life
- Malignant cells probably originate from follicular center B cells

Laboratory Features

White Blood Cells

- Variable, may be elevated in about 25% of cases
- May have slight eosinophilia

Red Blood Cells

- Anemia is rare

Platelets

- Thrombocytopenia is rare

Bone Marrow

- Required for staging
- Bone marrow infiltration is a serious manifestation

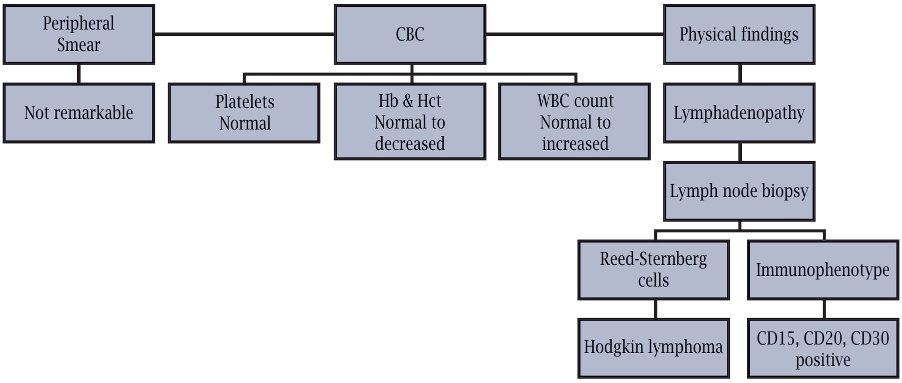
Immunophenotype

- CD20, CD30, and CD15 positive and most useful markers

Lymph Node Biopsy

- A large, intact lymph node is examined for the presence of Reed–Sternberg cells
  - Giant cells with large, eosinophilic, inclusion-like nucleoli; a thick, well-defined nuclear membrane; and page-staining chromatin
  - The classic cell has two-mirror image nuclei

Diagnostic Scheme


Peripheral Smear
CBC
Physical findings
Not remarkable
Platelets Normal
Hb & Hct Normal to decreased
WBC count Normal to increased
Lymphadenopathy
Lymph node biopsy
Reed-Sternberg cells
Immunophenotype
Hodgkin lymphoma
CD15, CD20, CD30 positive

Section C

Miscellaneous Disorders

CHAPTER 1

Quantitative Platelet Disorders

THROMBOCYTOPENIA

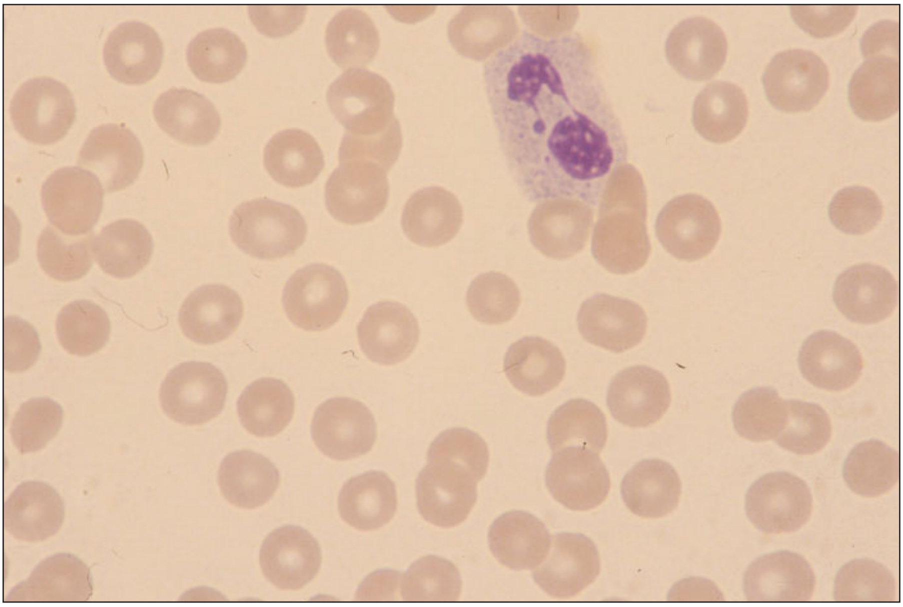


Figure IIC1-1

Peripheral blood smear.

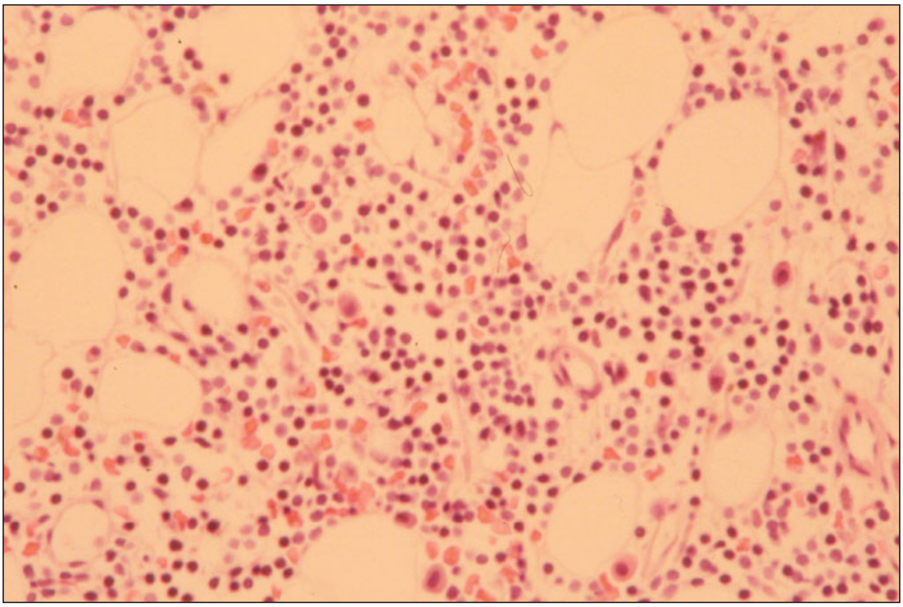


Figure IIC1-2

Bone marrow biopsy.

Clinical Features

- Petechiae and purpura
- Mild to moderate mucosal bleeding
- Gingival bleeding

Pathology

- Decreased megakaryocytopoiesis
  - Congenital
  - Acquired
    - Marrow damage
    - Marrow infiltration
- Ineffective production
  - Congenital
    - May-Hegglin anomaly
    - Wiscott-Aldrich syndrome
  - Acquired
    - Vitamin B_{12} or folate deficiency
- Sequestration or dilutional
  - Hypersplenism
  - Massive transfusion
- Increased destruction
  - Nonimmune
    - Consumption
    - Disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, vasculitis
  - Immune
    - Idiopathic thrombocytopenic purpura
      - Acute
      - Chronic

Laboratory Features

White Blood Cells

- Varies with etiology

Red Blood Cells

- Varies with etiology

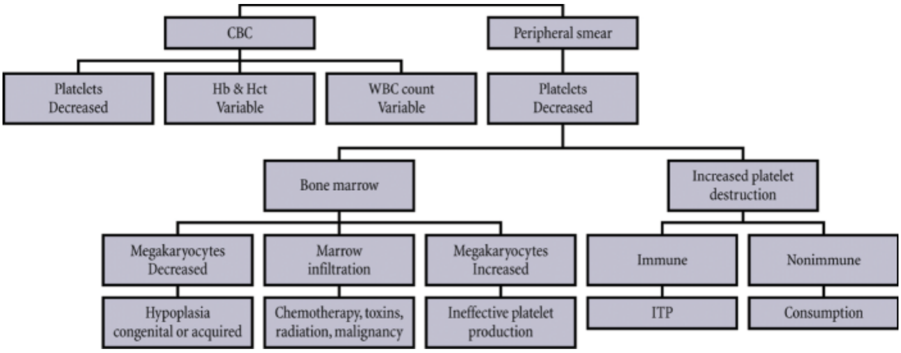
Platelets

- Decreased

Bone Marrow

- Increased, normal, or decreased megakaryocytes

Diagnostic Scheme


CBC
Peripheral smear
Platelets Decreased
Hb & Hct Variable
WBC count Variable
Platelets Decreased
Bone marrow
Increased platelet destruction
Megakaryocytes Decreased
Marrow infiltration
Megakaryocytes Increased
Immune
Nonimmune
Hypoplasia congenital or acquired
Chemotherapy, toxins, radiation, malignancy
Ineffective platelet production
ITP
Consumption

THROMBOCYTOSIS

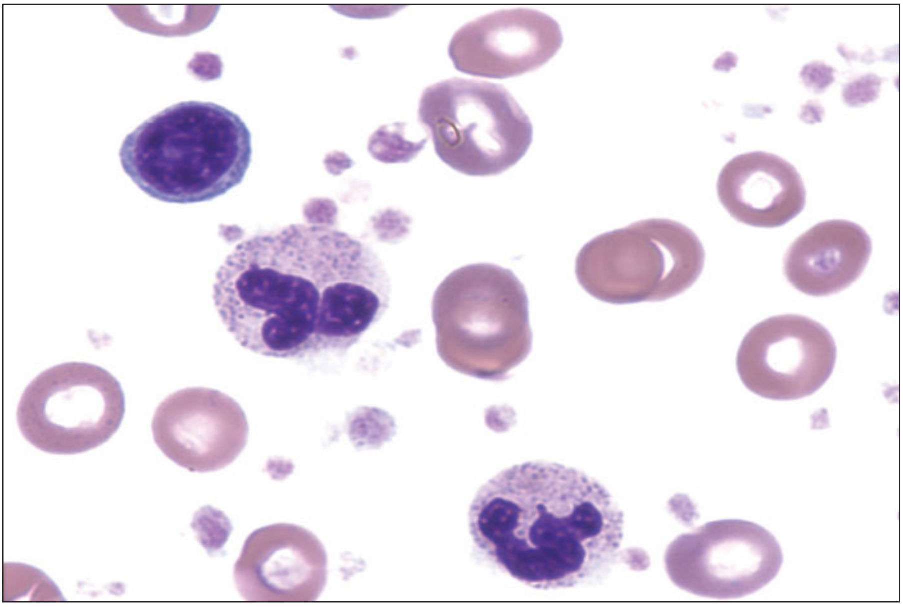


Figure IIC1-3

Peripheral blood smear.

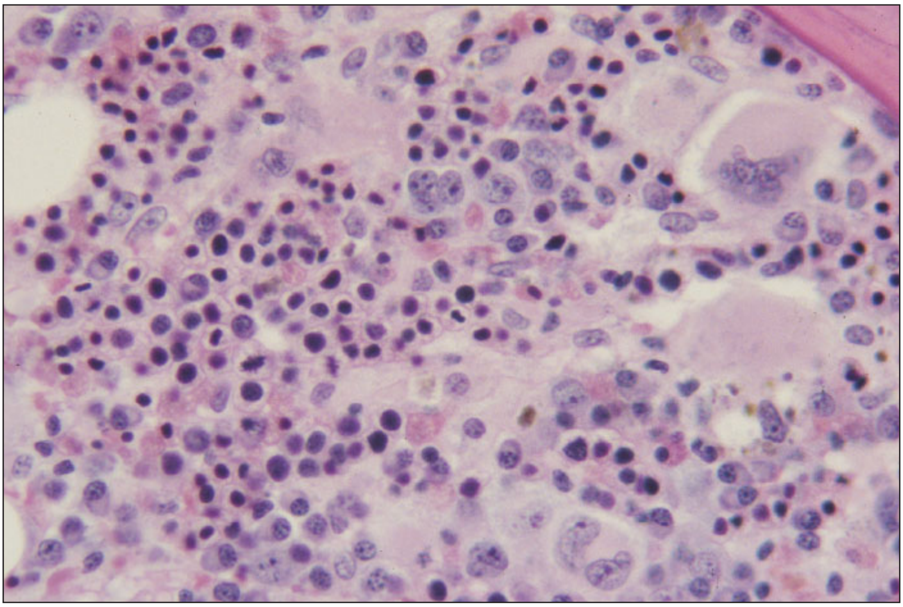


Figure IIC1-4

Bone marrow biopsy.

Clinical Features

- Reactive thrombocytosis is usually asymptomatic
- Autonomous thrombocytosis may be associated with bleeding and/or thrombosis

Pathology

- Secondary reactive thrombocytosis is associated with
  - Acute hemorrhage
  - Chronic inflammatory disorders
  - Hemolytic anemia
  - Severe iron deficiency
- Essential or primary thrombocythemia is associated with
  - Essential thrombocytosis
  - Other myeloproliferative diseases

Laboratory Features

White Blood Cells

- Varies with etiology

Red Blood Cells

- Varies with etiology

Platelets

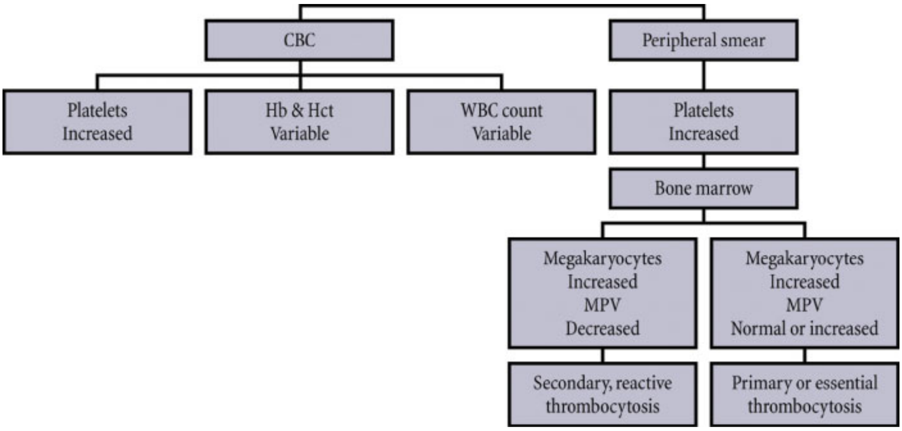
Secondary Thrombocytosis

- Platelets increased
- Megakaryocytes increased
- Mean platelet volume is decreased or increased

Primary or Essential Thrombocytosis

- Platelets greatly increased
- Megakaryocytes increased
- Mean platelet volume is increased (chronic myelogenous leukemia, chronic idiopathic myelofibrosis)
- Mean platelet volume is normal (essential thrombocythemia, polycythemia vera)

Diagnostic Scheme


CBC
Peripheral smear
Platelets Increased
Hb & Hct Variable
WBC count Variable
Platelets Increased
Bone marrow
Megakaryocytes Increased MPV Decreased
Megakaryocytes Increased MPV Normal or increased
Secondary, reactive thrombocytosis
Primary or essential thrombocytosis

CHAPTER 2

Hematologic Disease Associated With Microorganisms

BABESIOSIS

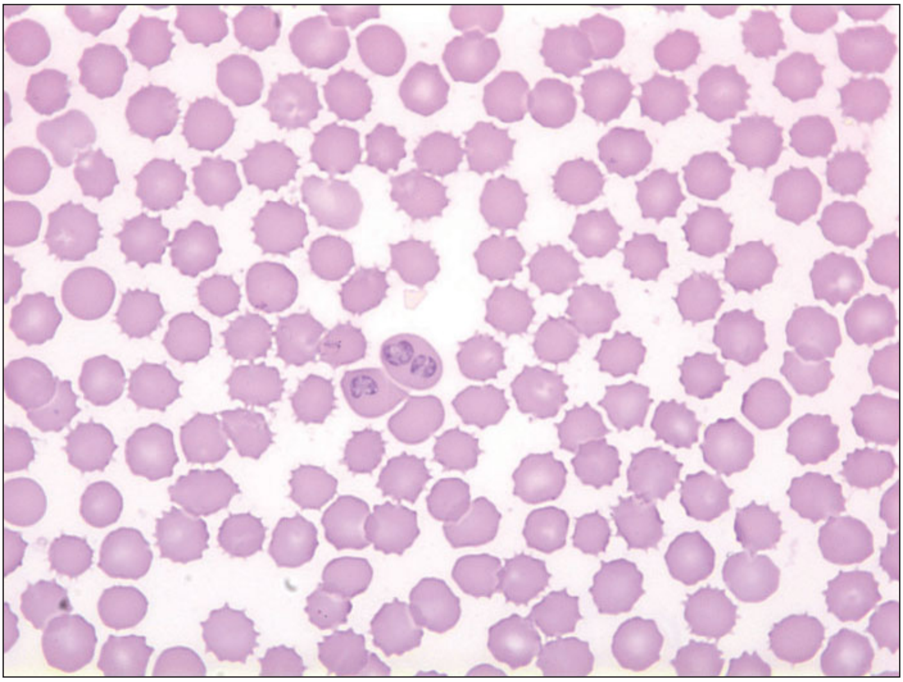


Figure IIC2-1

Peripheral blood smear.

Clinical Features

- May be asymptomatic from many months to years
- Malaise, fever, chills, fatigue, myalgia, and arthralgia
- Hepatosplenomegaly with jaundice
- Some fatalities have been reported

Pathology

- Rodents are the main reservoir, but some human infections with cattle and dog species of *Babesia* have been reported
- *Babesia* are major pathogens in wild and domestic animals that nearly destroyed the American cattle industry during the late nineteenth century
- Human infections are still rare and have similar epidemiology to Lyme disease but are less widely spread
- Transmitted by the bite of the deer tick but can be transmitted transplacentally and by blood transfusion

Laboratory Features

White Blood Cells

- Mild neutropenia

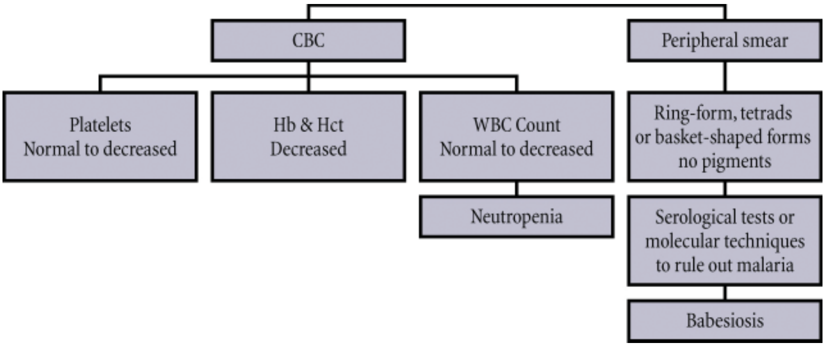
Red Blood Cells

- Mild to severe hemolytic anemia

Platelets

- Thrombocytopenia may occur
- *Babesia* organisms found on the blood smear
- Intraerythrocytic ring-shaped or pleomorphic parasites (piroplasms)
- Extraerythrocytic parasites found
- Unlike malaria, there is no pigment

Diagnostic Scheme


CBC
Peripheral smear
Platelets Normal to decreased
Hb & Hct Decreased
WBC Count Normal to decreased
Neutropenia
Ring-form, tetrads or basket-shaped forms no pigments
Serological tests or molecular techniques to rule out malaria
Babesiosis

BORRELIOSIS

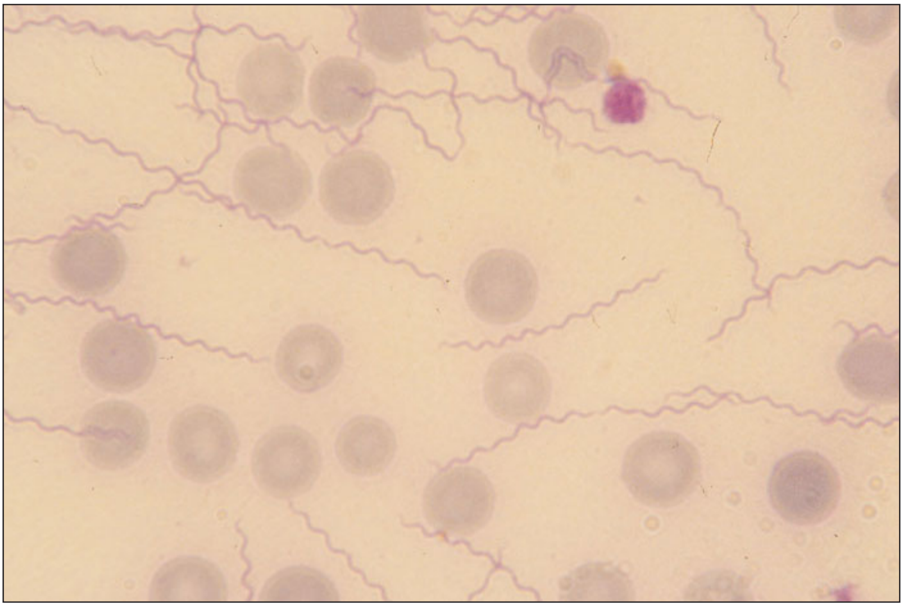


Figure IIC2-2

Peripheral blood smear.

Clinical Features

- High fever, shaking chills, delirium, headache, and muscle aches
- Cyclical pattern of symptoms corresponds to parasite development
- Pain in bones and joints
- Hepatosplenomegaly with tenderness
- Jaundice

Pathology

- Several species of *Borrelia* spirochetes
- Enter the body through the bite of a tick or through contamination of abraded skin with materials from crushed body lice

Laboratory Features

White Blood Cells

- Leukocytosis
- Neutrophilia

Red Blood Cells

- Not remarkable

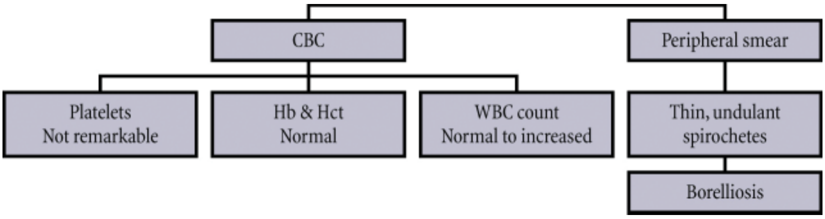
Platelets

- Not remarkable

Presence of Spirochetes in Blood During a Febrile Episode

- Thin, undulant, and overtly spiral organisms
- Located between red blood cells

Diagnostic Scheme


CBC
Peripheral smear
Platelets Not remarkable
Hb & Hct Normal
WBC count Normal to increased
Thin, undulant spirochetes
Borelliosis

CANDIDIASIS

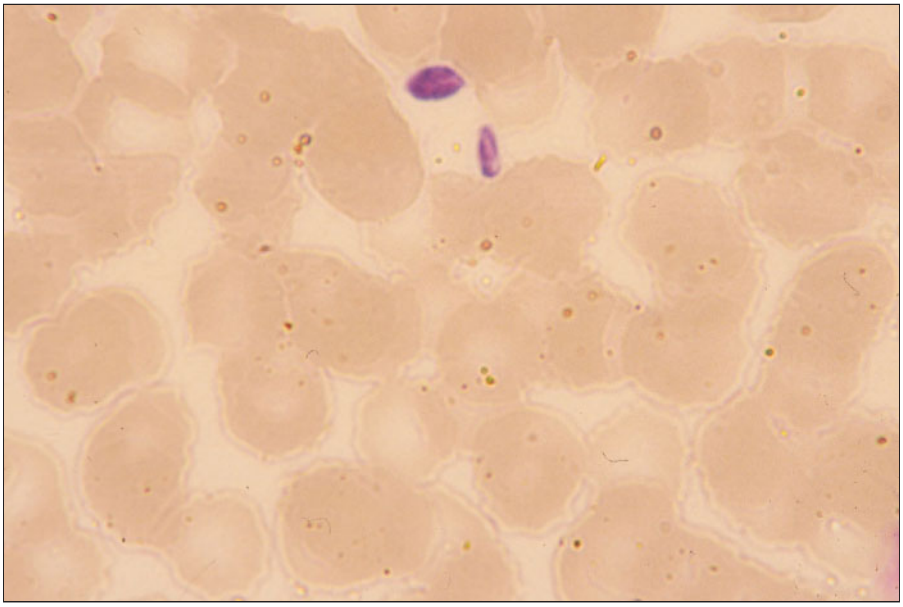


Figure IIC2-3

Peripheral blood smear.

Clinical Features

- Dysphagia, cough, itching, and burning
- Discharge—depends on primary location of infection
- Fever, chills, and headache
- May include shock, renal shutdown, and disseminated intravascular coagulation

Pathology

- Species of *Candida,* which are commensal organisms
- *Candida albicans* is the most common agent
- Immunocompromised people are at risk for infection
- Persons treated with broad-spectrum antibiotics and corticosteroids are at risk

Laboratory Features

White Blood Cells

- Leukocytosis

Red Blood Cells

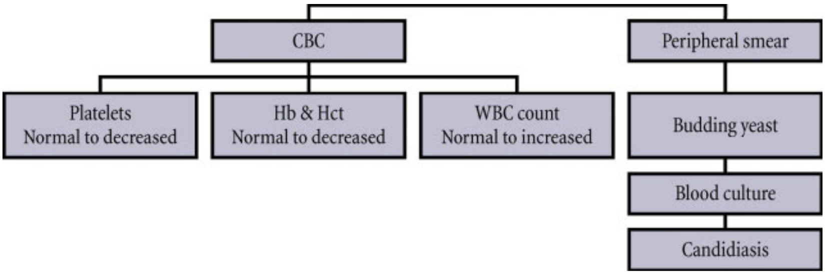
- Anemia develops in severe infections

Platelets

- Thrombocytopenia may develop

Budding Yeast With Pseudo or True Hyphae Can Be Observed in the Blood

Diagnostic Scheme


CBC
Peripheral smear
Platelets Normal to decreased
Hb & Hct Normal to decreased
WBC count Normal to increased
Budding yeast
Blood culture
Candidiasis

FILARIASIS

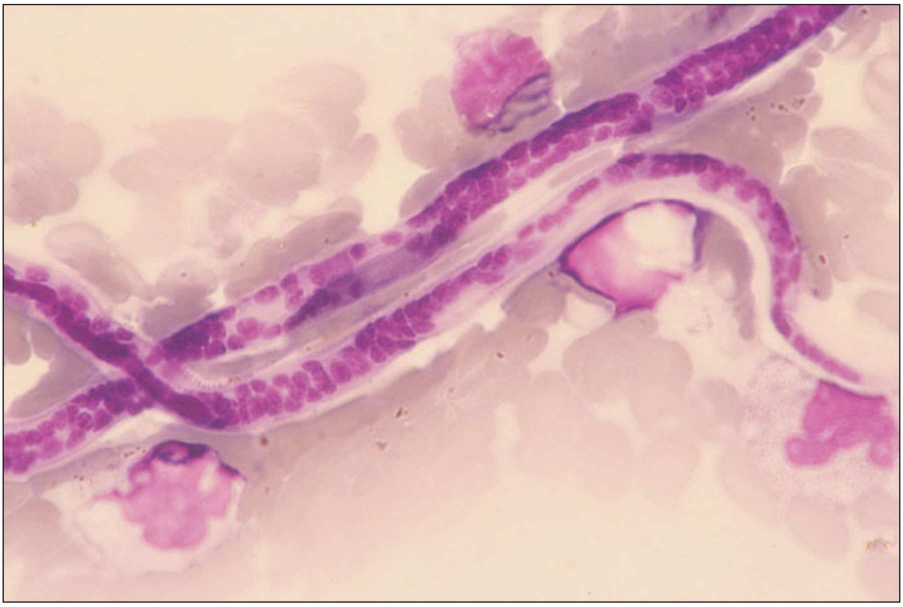


Figure IIC2-4

Peripheral blood smear.

Clinical Features

- Tissue-dwelling nematodes producing larvae that appear in blood, skin, and serous fluids
- May be asymptomatic
- Lymphadenitis to disruption of lymphatic vessels or drainage of lymph fluid
- Low-grade fever
- Maculopapular rash
- Urticaria

Pathology

- May be caused by *Wuchereria bancrofti, Brugia malayi, Brugia timori,* or *Loa Loa*
- Spread by mosquitoes or tabanid fly when infective larvae escape from the mosquito, enter the puncture wound, and migrate to the lymphatics
- Adult worms develop in the lymphatics
- Gravid females produce microfilariae that circulate in blood
- Bancroftian filariasis present in tropical areas of Africa, Asia, the Pacific, and the Americas
- Brugian filariasis is found in South and Southeast Asia
- Loiasis is confined to the rain forest belt of western and central Africa and equatorial Sudan

Laboratory Features

White Blood Cells

- Normal to increased
- Eosinophilia possible

Red Blood Cells

- Not remarkable

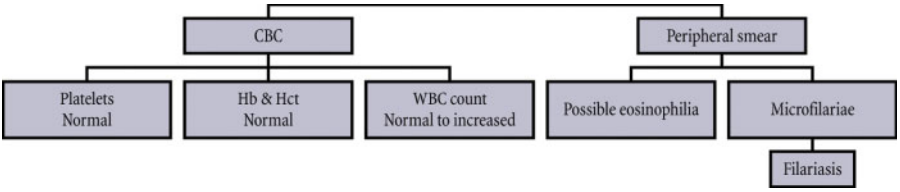
Platelets

- Not remarkable

Microfilariae in Blood May Be Seen on Stained Thick Films

- Species identification may be made by microfilaria morphology

Diagnostic Scheme


CBC
Peripheral smear
Platelets Normal
Hb & Hct Normal
WBC count Normal to increased
Possible eosinophilia
Microfilariae
Filariasis

HISTOPLASMOSIS

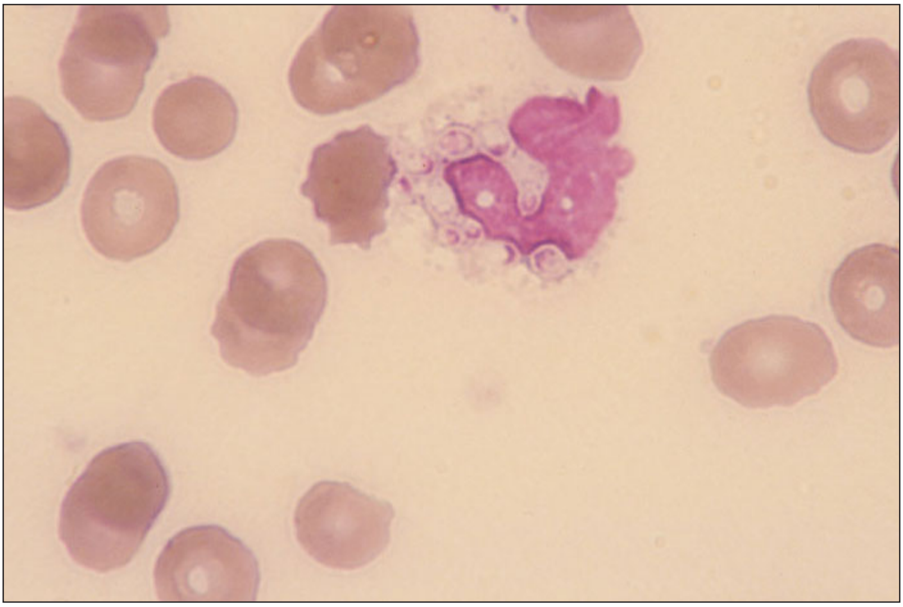


Figure IIC2-5

Peripheral blood smear.

Clinical Features

- Three stages
  - Acute primary
    - Asymptomatic to fever, cough, and malaise
  - Progressive disseminated
    - Hepatosplenomegaly, lymphadenopathy, or gastrointestinal ulcerations, fatigue, weakness, malaise
  - Chronic cavitary
    - Pulmonary lesions, worsening cough, dyspnea, and decreasing pulmonary function

Pathology

- Infection occurs worldwide; the endemic areas in the United States are the Ohio and Mississippi river valleys
- *Histoplasma capsulatum* is the causative agent
- Inhalation of spores in soil or dust contaminated with bird or bat droppings is the mode of exposure

Laboratory Features

White Blood Cells

- Normal to increased

Red Blood Cells

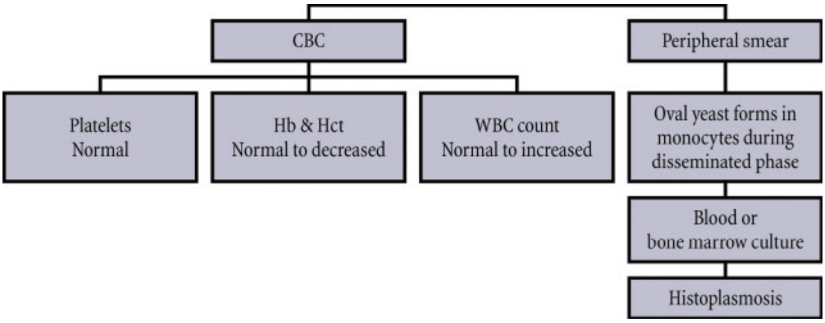
- Anemia in severe infections

Platelets

- Not remarkable

Small Oval Yeast Forms May Be Seen Within Macrophages or Monocytes on Peripheral Blood, Bone Marrow, or Buffy Coat Smears

Diagnostic Scheme


CBC
Peripheral smear
Platelets
Normal
Hb & Hct
Normal to decreased
WBC count
Normal to increased
Oval yeast forms in monocytes during disseminated phase
Blood or bone marrow culture
Histoplasmosis

LEISHMANIASIS

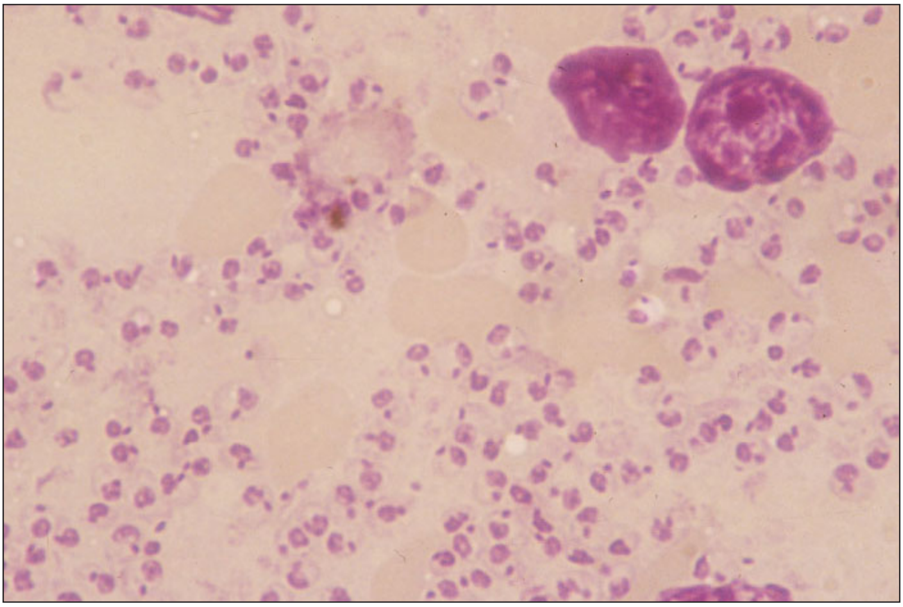


Figure IIC2-6

Splenic biopsy.

Clinical Features

- Three forms exist:
  - Visceral leishmaniasis (kala-azar, dumdum fever)
    - Irregular fever, hepatosplenomegaly, and emaciation
  - Cutaneous leishmaniasis (oriental or tropical sore)
    - Sharply demarcated skin lesion at the site of infective bite
    - Multiple lesions are rare and take months to heal
  - Mucocutaneous leishmaniasis (espundia)
    - Primary cutaneous ulcer appears but can metastasize to nasopharyngeal tissue and cause gross mutilations of the nose, palate, maxillary, etc.

Pathology

- Blood and tissue flagellates that are zoonotic infections from dogs, rodents, and other reservoirs

Visceral Leishmaniasis

- Present worldwide in tropical and some temperate areas
- Caused by *Leishmania donovani* complex
- Transmitted by the bite of sandflies
- Parasites are disseminated from the skin to the lymph nodes, spleen, liver, and bone marrow
- Parasites are intracellular in macrophages
- Highly fatal without treatment

Cutaneous Leishmaniasis

- Occurs in southern Europe, Asia, Africa, the Middle East, Mexico, and Central and South America
- Causative agents are *Leishmania major, Leishmania tropica, Leishmania mexicana,* and *Leishmania braziliensis*
- Does not respond well to treatment, but once ulcers are healed, permanent immunity results

Mucocutaneous Leishmaniasis

- Caused mainly by *Leishmania viannia braziliensis*
- Parasites develop in nasopharyngeal macrophages
- Greatly feared because of gross deformities
- All forms of leishmaniasis are difficult to treat

Laboratory Features

White Blood Cells

- Leukopenia may occur in chronic forms

Red Blood Cells

- Anemia may develop in chronic forms

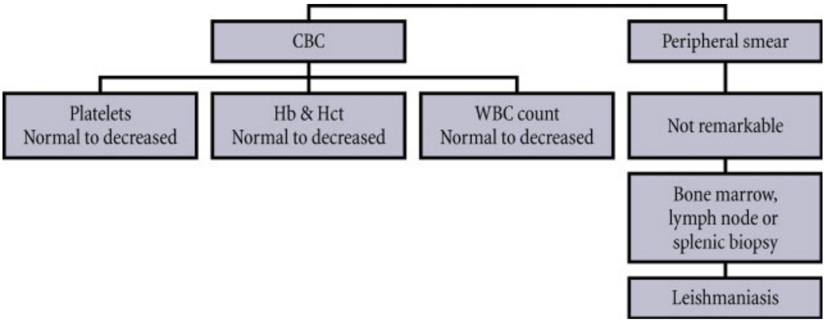
Platelets

- Thrombocytopenia may develop in chronic forms

The Intracellular Amastigotes May Be Seen in Stained Smears Containing Macrophages (i.e., bone marrow, splenic punctures)

- More difficult to see in cutaneous lesions

Diagnostic Scheme


CBC
Peripheral smear
Platelets
Normal to decreased
Hb & Hct
Normal to decreased
WBC count
Normal to decreased
Not remarkable
Bone marrow,
lymph node or
splenic biopsy
Leishmaniasis

MALARIA

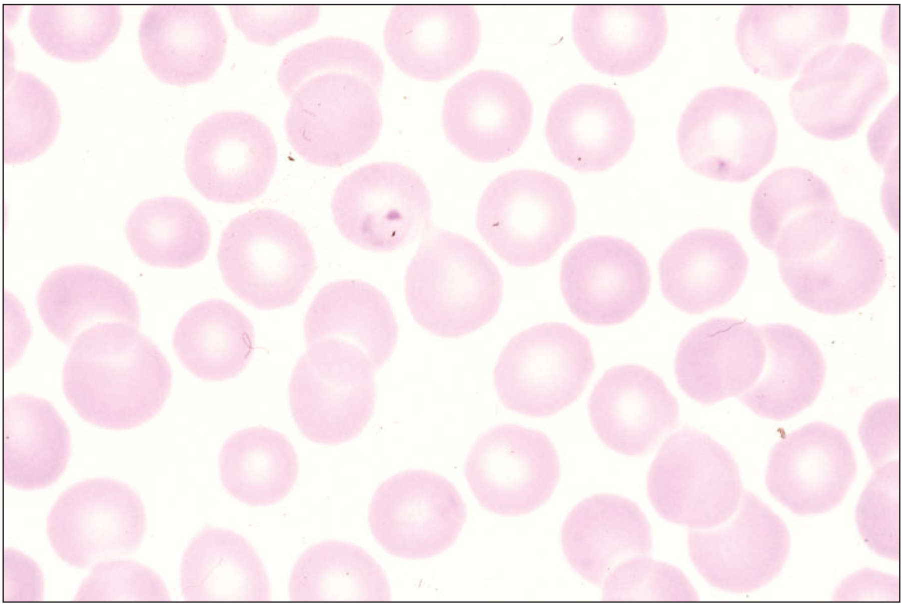


Figure IIC2-7

Peripheral blood smear.

Clinical Features

- Malaise, chills, and fever
- Thready pulse, headache, and nausea
- Anemia
- Jaundice
- Diarrhea
- Hepatosplenomegaly

Pathology

- Malaria is the second most important disease in the world (500 million cases per year, with 1–3 million deaths)
- Endemic in Africa, South and Southeast Asia, Central America, and northern South America
- Caused by four different species: *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae*
- Transmitted by the female *Anopheles* mosquitoes, which are strictly nighttime feeders

Laboratory Features

White Blood Cells

- Not remarkable

Red Blood Cells

- Hemolytic anemia

Platelets

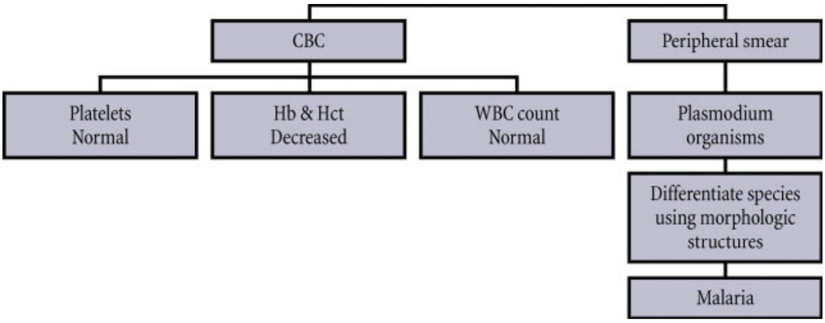
- Not remarkable

Plasmodium Organisms May Be Found on Thin and Thick Peripheral Blood Smears

- Species diagnosis is made by ring-stage morphology

New Serologic Tests Are Now Becoming Available

Diagnostic Scheme


CBC
Peripheral smear
Platelets Normal
Hb & Hct Decreased
WBC count Normal
Plasmodium organisms
Differentiate species using morphologic structures
Malaria

TOXOPLASMOSIS

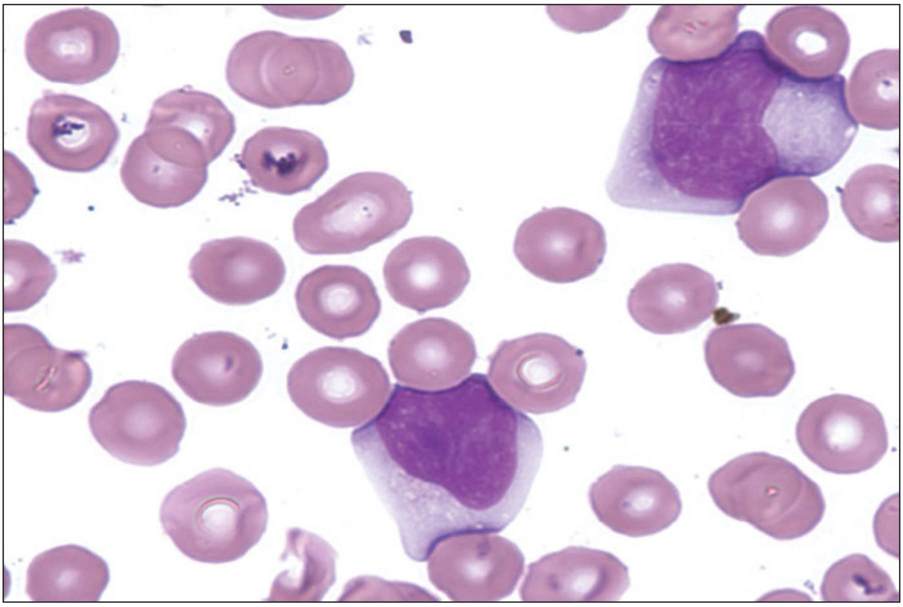


Figure **IIC2-8**

Peripheral blood smear.

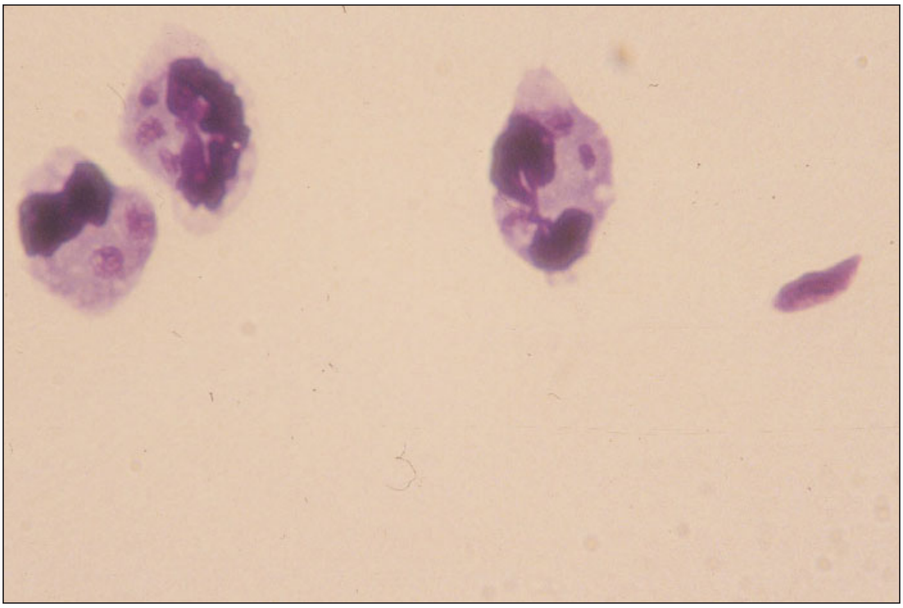


Figure **IIC2-9**

Lymph node impression.

Clinical Features

- Usually asymptomatic
- Principal health risk is to neonates of infected women, and it is an important cause of death in patients with AIDS
- May cause malaise, fever, myalgia, and pharyngitis
- Lymphadenopathy and hepatosplenomegaly
- Severe form—pneumonitis, myocarditis, meningoencephalitis, high fever, and chills

Pathology

- Immunocompromised patients may be at risk for a severe form of the infection
- Caused by *Toxoplasma gondii,* which is a ubiquitous protozoan parasite of birds and mammals
- Ingestion of oocysts from cat feces is the most common mode of oral infection
- Undercooked meats may be infective
- Can be transmitted transplacentally

Laboratory Features

White Blood Cells

- Lymphocytosis
- Atypical lymphocytes

Red Blood Cells

- Not remarkable

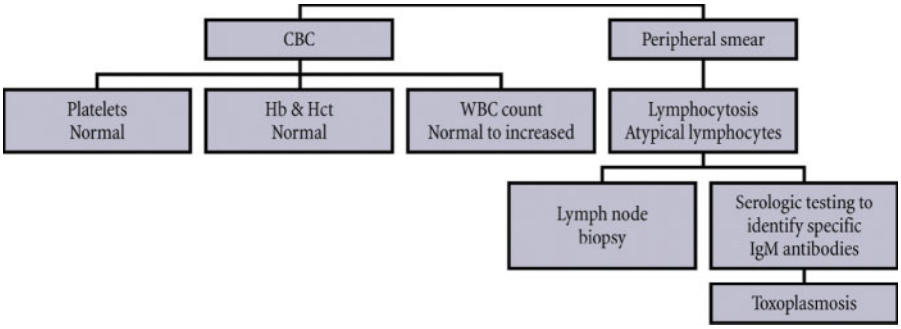
Platelets

- Not remarkable

Cluster of Tachyzoites May Be Observed in Tissue Sections or Impression Smears

- Organisms may be seen in the white blood cells or macrophages in the bone marrow

Diagnostic Scheme


CBC
Peripheral smear
Platelets Normal
Hb & Hct Normal
WBC count Normal to increased
Lymphocytosis Atypical lymphocytes
Lymph node biopsy
Serologic testing to identify specific IgM antibodies
Toxoplasmosis

TRYPANOSOMIASIS

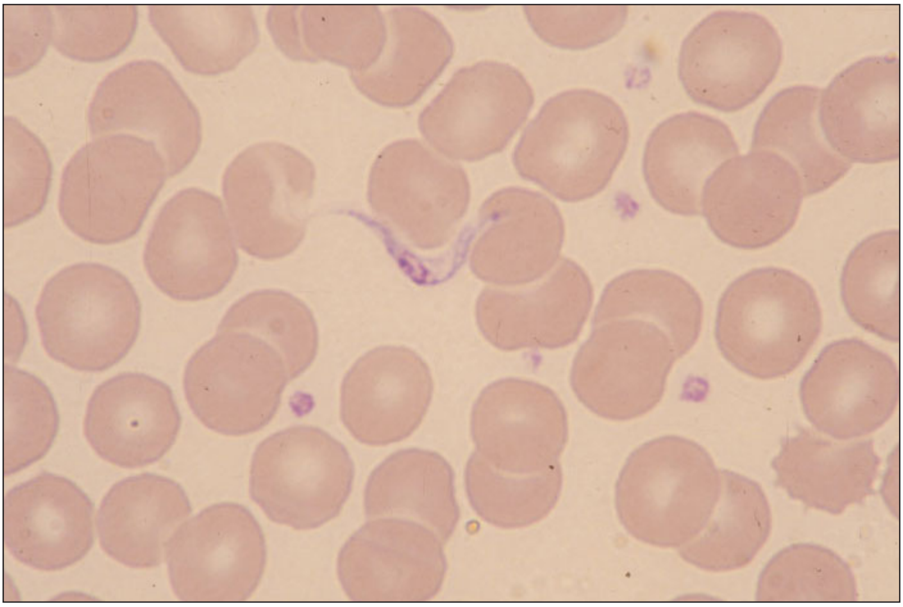


Figure IIC2-10

Clinical Features

African Trypanosomiasis (African Sleeping Sickness)

- Papule develops and resolves spontaneously
- Fever, headache, edematous swellings, and red rash
- Lymphadenopathy
- Central nervous system involvement—headache, personality changes, somnolence, tremor, ataxia, and coma

American Trypanosomiasis (Chagas' Disease)

- Initial infection is usually asymptomatic
- May have indurated skin lesion at the site of entry
- Fever and malaise
- Generalized lymphadenopathy and hepatosplenomegaly
- Major cause of heart disease in South America, chronic cardiomyopathy occurs in some cases

Pathology

African Trypanosomiasis

- Caused by *Trypanosoma brucei gambiense* in western and central Africa
- Caused by *Trypanosoma brucei rhodesiense* in eastern Africa
- Transmitted by tsetse flies
- May be transmitted by blood transfusion

American Trypanosomiasis

- Caused by *Trypanosoma cruzi*
- Transmitted by triatomine (reduviid) bugs
- Infected bugs deposit feces containing the organisms while feeding
- The organisms enter through the bite and invade macrophages at the site of entry
- Eventually they reach other cells of the reticuloendothelial system
- Primary damage is to neuroconductivity of the heart, esophagus, and colon
- Can be transmitted by blood transfusion

Laboratory Findings

White Blood Cells

- Not remarkable

Red Blood Cells

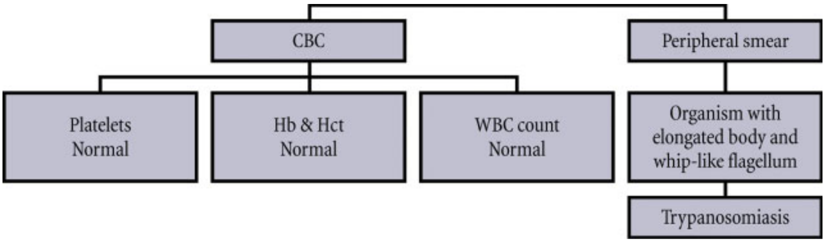
- Not remarkable

Platelets

- Not remarkable

Organisms May Be Observed in Thin and Thick Smears of Peripheral Blood During the Acute Phase of Infection

Diagnostic Scheme


CBC
Peripheral smear
Platelets Normal
Hb & Hct Normal
WBC count Normal
Organism with elongated body and whip-like flagellum
Trypanosomiasis

CHAPTER 3

Reticuloendothelial System Storage Disorders

GAUCHER DISEASE

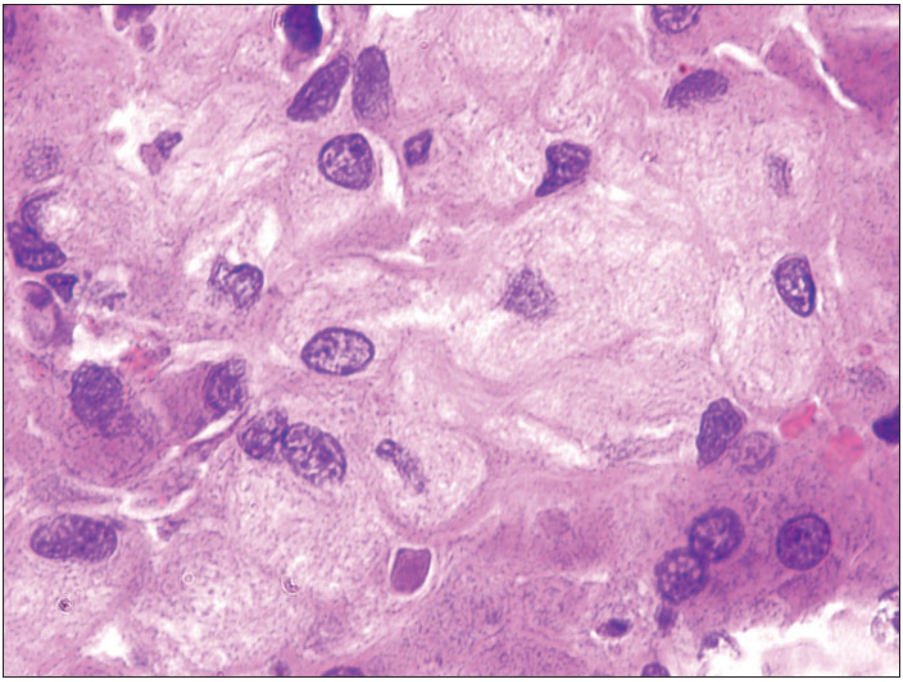


Figure IIC3-1

Bone marrow smear.

Clinical Features

- Splenomegaly
- Hepatomegaly
- Destruction of bone
- Pigmentation of skin in exposed areas
- Purpura and abnormal bleeding

Pathology

- Most common storage disease
- Inherited as an autosomal recessive trait
- Deficiency of beta-glucocerebrosidase
- Accumulation of glucocerebroside in macrophages of lymphoid tissue, spleen, liver, and bone marrow

Laboratory Features

White Blood Cells

- Leukopenia (2.0–3.0 × 10^9/L)
- Relative lymphocytosis

Red Blood Cells

- Normocytic/hypochromic anemia

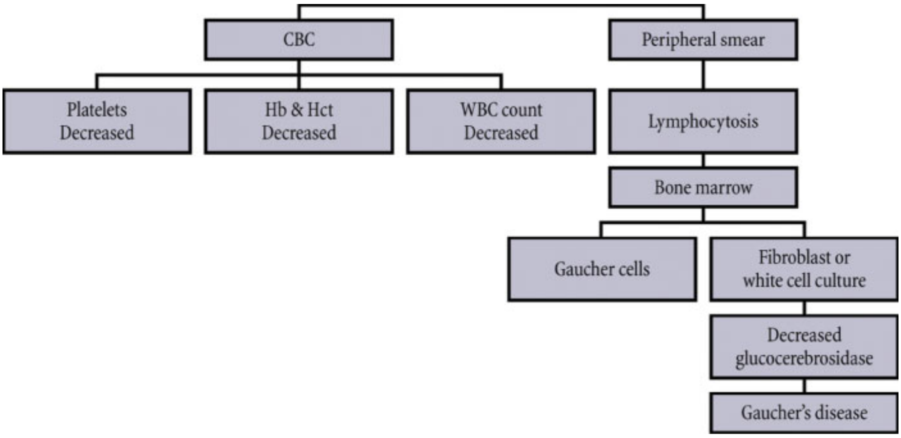
Platelets

- Moderate thrombocytopenia (50–100 × 10^9/L)

Bone Marrow

- Presence of Gaucher cells in bone marrow, spleen, and liver
    - Cell is large, with relatively small eccentric nucleus with coarsely clumped cytoplasm that is filled with a fibrillar pale-staining lipid

Diagnostic Scheme


CBC
Peripheral smear
Platelets Decreased
Hb & Hct Decreased
WBC count Decreased
Lymphocytosis
Bone marrow
Gaucher cells
Fibroblast or white cell culture
Decreased glucocerebrosidase
Gaucher's disease

MUCOPOLYSACCHARIDOSIS

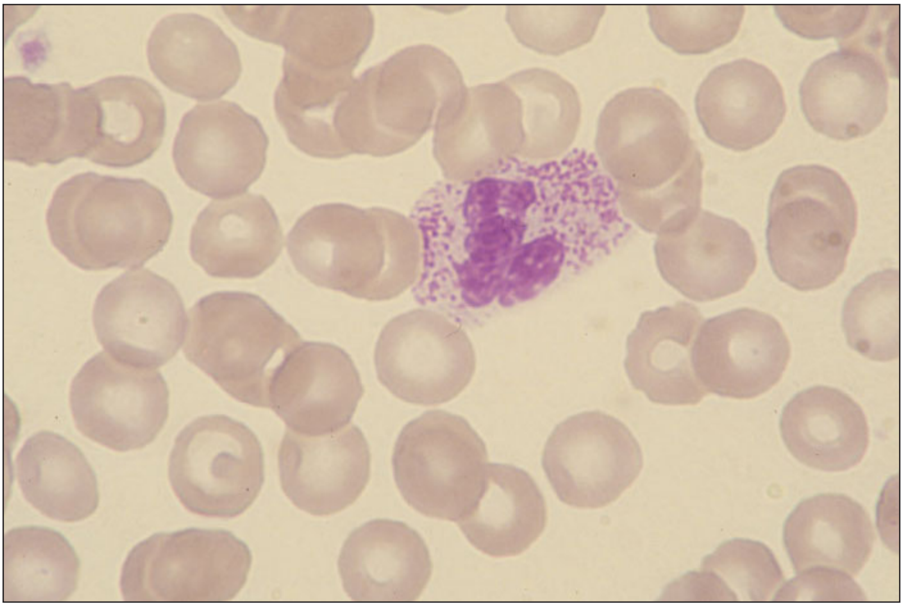


Figure IIC3-2

Peripheral blood smear.

Clinical Features

- Coarse facial features—flat nose and thick lips
- Skeletal abnormalities, including bone dysplasias and joint movement restriction
- Dwarfism
- Neurologic manifestations
  - Psychomotor retardation
  - Deafness
  - Ataxia
  - Mental status disturbances
- Severity varies with the type of mucopolysaccharide present
- Hepatosplenomegaly

Pathology

- A group of inherited diseases with enzyme deficiencies
- Excessive accumulation of mucopolysaccharides in body tissues
  - Arteries
  - Skeleton
  - Eyes
  - Joints
  - Skin
  - Liver
  - Bone marrow
  - Central nervous system
- Inherited as autosomal recessive genes with the exception of Hunter's syndrome, which is X-linked
- Depending on enzyme deficiency, different syndromes occur
  - Hurler's
  - Hunter's
  - Sanfilippo's
  - Morquio's (no Alder-Reilly inclusions seen)
  - Scheie's Maroteaux-Lamy
  - Sly's

Laboratory Features

White Blood Cells

- Presence of Alder-Reilly bodies in neutrophils, eosinophils, and basophils
- Inclusions may occasionally be seen in lymphocytes and monocytes

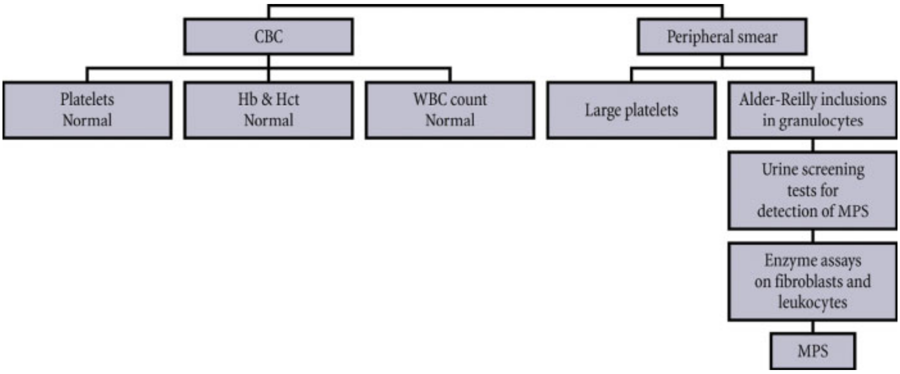
Red Blood Cells

- Not remarkable

Platelets

- Abnormally large

Diagnostic Scheme


CBC
Peripheral smear
Platelets Normal
Hb & Hct Normal
WBC count Normal
Large platelets
Alder-Reilly inclusions in granulocytes
Urine screening tests for detection of MPS
Enzyme assays on fibroblasts and leukocytes
MPS

NIEMANN-PICK DISEASE

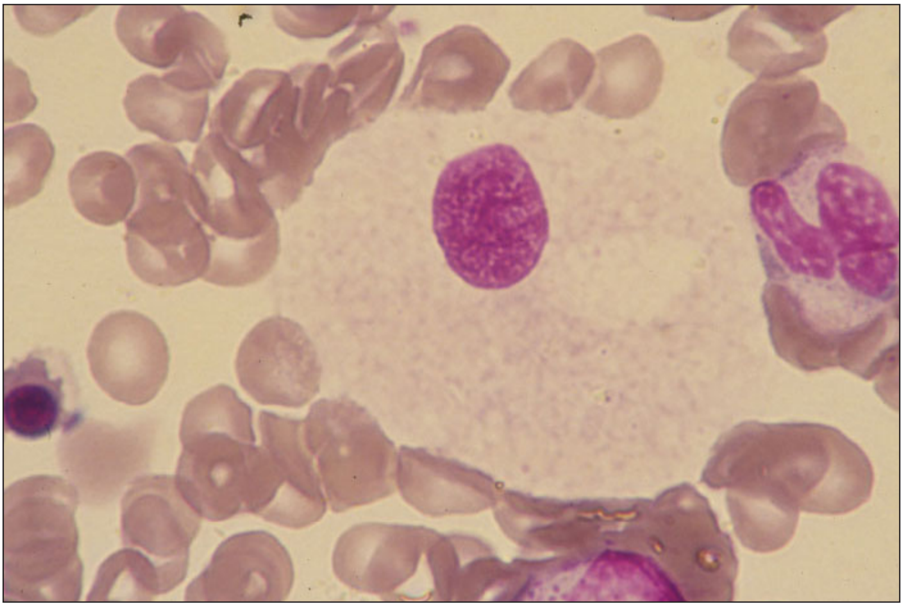


Figure IIC3-3

Bone marrow smear.

Clinical Features

- Splenomegaly
- Hepatomegaly
- Severely impaired development
- About one-third have a cherry-red spot on the macula of the retina
- It affects girls more often than boys

Pathology

- An autosomal recessive inherited disorder
- Deficiency of sphingomyelinase
- Accumulation of sphingomyelin in macrophages in the lymphoid system

Laboratory Features

White Blood Cells

- Leukopenia may occur
- Monocytes and lymphocytes may show characteristic vacuoles

Red Blood Cells

- Mild anemia

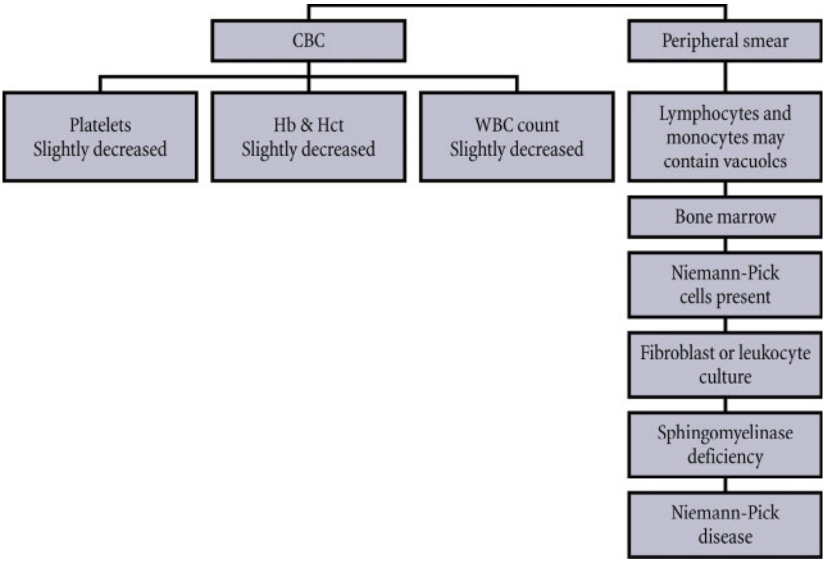
Platelets

- Mild thrombocytopenia

Bone Marrow

- Finding Niemann-Pick cells in bone marrow or other tissues
  - These cells are filled with droplets of sphingomyelin material

Diagnostic Scheme


CBC
Peripheral smear
Platelets Slightly decreased
Hb & Hct Slightly decreased
WBC count Slightly decreased
Lymphocytes and monocytes may contain vacuoles
Bone marrow
Niemann-Pick cells present
Fibroblast or leukocyte culture
Sphingomyelinase deficiency
Niemann-Pick disease

SEA-BLUE HISTIOCYTOSIS

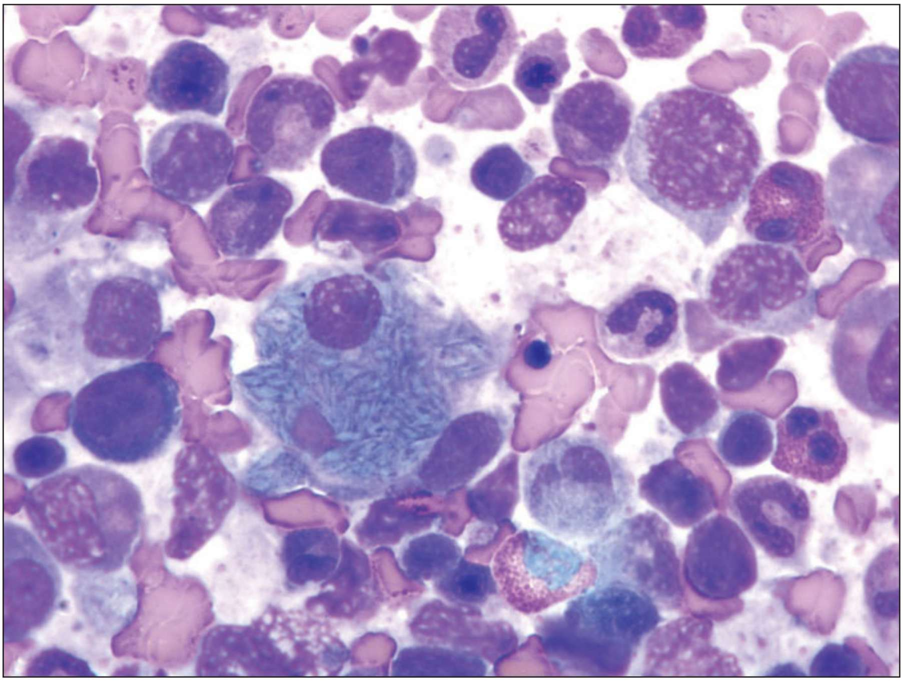


Figure IIC3-4

Bone marrow smear.

Clinical Features

- Splenomegaly
- Hepatomegaly
- Purpura seen in about half of the cases
- Occasional neurologic damage

Pathology

- Familial disorder in which macrophages contain blue or blue-green granules in the cytoplasm
- No specific enzyme deficiency
- Course of the disease is usually benign
- An acquired type of this disease is associated with a number of conditions

Laboratory Features

White Blood Cells

- Not remarkable

Red Blood Cells

- Not remarkable

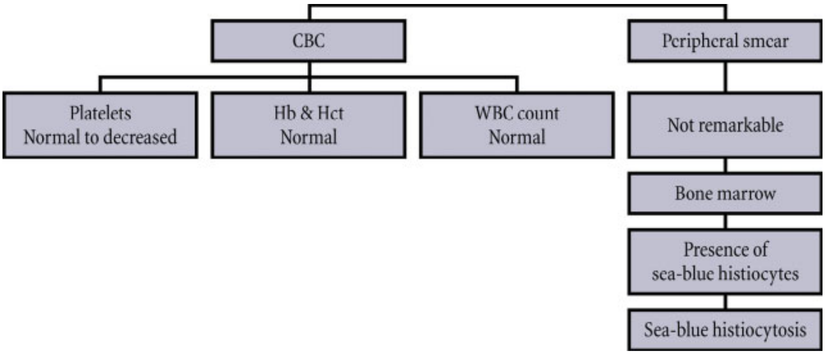
Platelets

- Normal to decreased

Bone Marrow

- Sea-blue histiocytes are found in bone marrow and spleen
  - Large cells
  - Eccentric nucleus
  - Cytoplasm contains blue or blue-green granules

Diagnostic Scheme


CBC
Peripheral smear
Platelets
Normal to decreased
Hb & Hct
Normal
WBC count
Normal
Not remarkable
Bone marrow
Presence of
sea-blue histiocytes
Sea-blue histiocytosis

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